Chapter 6

Lipid Abnormalities in Hemodialysis Patients

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1. Introduction

Approximately 50% of hemodialysis (HD) patients die from cardiovascular events. One of the main risk factors for cardiovascular events is hyperlipidemia. Progressive renal failure is associated with lipoprotein abnormalities and dyslipidemia. However, dyslipidemia may not appear as hyperlipidemia (a rise in plasma cholesterol and/or low-density lipoprotein (LDL)) in the majority of HD patients. Uremic dyslipidemia has an abnormal apolipoprotein profile and composition. It is characterized by reduced concentrations of apo A-containing lipoproteins in high-density lipoprotein (HDL) and increased concentrations of intact or partially metabolized triglyceride-rich apo B-containing lipoproteins in very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL) and LDL.

Common lipid abnormality in HD patients is hypertriglyceridemia. Other lipid abnormalities seen in HD patients are high serum lipoprotein levels and a decrease in HDL levels. Hypertriglyceridemia is caused by increased production of Apo B protein and a marked decrease in the metabolism of VLDL, primarily as a result of decreased endothelial cell debilitation of VLDL.

The lipoprotein abnormalities in HD patients are thought to be a significant factor in increased atherosclerosis. Serum total cholesterol, and particularly LDL-cholesterol, is known to be correlated with increased cardiovascular mortality in the general population. A similar correlation has also been reported in dialysis patients. However, it is today generally agreed that in the HD patient group, a low LDL cholesterol level is correlated with malnutrition and increased mortality.

Until recently, the treatment of hyperlipidemia in the HD patient group was based on adult hyperlipidemia guidelines, and it was generally thought that the approach to treatment and results in the general population would yield similar results in the HD patient group. However, in the same way that lipid abnormalities in the HD patient group differ from the gen-

eral population, there are also various differences in terms of medical treatment. Treatment of hypertriglyceridemia, the most frequently observed lipid abnormality in this patient group, is advised since at above 500 mg/dl it can give rise to complications such as pancreatitis. Lifestyle changes plus fibrate or nicotinic acid are recommended for treatment of hypertriglyceridemia. However, medical treatment must be provided on the basis of a profit and loss calculation, bearing in mind the side-effects (myositis and rhabdomyolysis). The calculation of non-HDL cholesterol, used to measure the level of remnant lipoproteins, is useful in situations where LDL cholesterol is normal and triglyceride levels high. Studies have been published suggesting that this can initially reduce the frequency of cardiovascular events associated with the use of statin in the treatment of a high LDL cholesterol level. However, the AURORA study, a large prospective, randomized study published in 2009, showed that although rosuvastatin lowered LDL cholesterol in the HD patient group it did not lead to a decrease in cardiovascular mortality. From this important study and other similar research, different approaches may be expected in both the adult hyperlipidemia guideline and in guidelines regarding the HD patient group from those in the general population.

1.1. Vascular calcification

Cardiovascular diseases are the principal cause of death in HD patients. Widespread vascular calcification especially in the coronary arteries is one of the main causes of cardiovascular disease (Braun et al., 1996; London et al., 2003, Sigrist et al., 2007). Vascular calcification can be observed in two regions of the arterial structure, the intima and the media (Shanahan et al., 1999). Arterial intimal calcification (AIC) is generally associated with atherosclerotic lesions, and with plaque formation and the development of occlusive lesions (Shanahan et al., 1999). AIC may also be observed in patients with normal renal function, and calcification of the atherosclerotic plaque increases the frequency of MI and thrombotic complications. Arterial medial calcification (AMC) is seen in muscular arteries and leads to a reduction in vascular wall elasticity more than to occlusive lesions (London et al., 2003). AMC is more associated with uremia. Both AIC and AMC may be observed in HD patients.

Although vascular calcification was determined in uremic patients many years ago, research into its etiopathology is still on-going. Factors held responsible in the etiopathology today include a rise in osteogenic proteins such as osteocalcin, osteonectin, alkaline phosphatase and collagen-I, low levels of calcification inhibitors such as matrix Gla-protein, osteopontin, fetuin, pyrophosphate and osteoprotegerin, genetic factors, use of high-dose vitamin D, high Ca-P levels, hyperparathyroidism, inflammation and hyperlipidemia (Fukagawa & Kazama, 2007; Rutsch et al., 2011; Shantouf et al., 2009; Slatopolsky et al., 1980; Tamashiro et al., 2001; Tukaj et al., 2000).

As previously discussed, while classic cardiovascular risk factors are more associated with development of AIC, uremia and associated factors are more involved in the development of AMC. London et al.'s study on the subject determined that high phosphorus and low albunim levels and excessive Ca consumption represented risk factors for AIC, in addition to classic risk factors such as advanced age, a history of atherosclerotic disease, cigarette use and a history of DM and high LDL and CRP levels. They also showed that in addition to

these classic risk factors, parameters more associated with HD and prolonged HD were influential in the development of AMC. In addition, in contrast to AIC, AMC may also be observed at early ages (London et al., 2003)

While definitive diagnosis of vascular calcification is made with histopathological examination, since this is not possible in clinical practice, the K-DIGO guideline recommends x-ray imaging and echocardiographic examination in the diagnosis of vascular and valvular calcification (Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. 2010). In conclusion, the term vascular calcification is used for two different entities in HD patients, AIC and AMC. The reason why the term vascular calcification is used to refer to both these clinical conditions is that both AIC and AMC can frequently be seen in the HD patient group and that differentiation cannot be performed with routine examinations. However, what must not be forgotten is that although they appear to be similar, there are various differences in the etiology, clinical reflections and approaches to treatment in these two clinical conditions. While improvement of atherosclerotic risk factors (hyperlipidemia, etc.) and sufficient dialysis may be beneficial in AIC, sufficient dialysis is of particular benefit in the treatment and prevention of AMC

2. The relation between dyslipidemia and cardiovascular events

Chronic kidney disease (CKD) is a significant health problem, the prevalence of which is increasing all over the world. The main cause of death in this patient population is cardiovascular disease (CVD)-related mortality (K/DOQI Workgroup. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients, 2005; Silva et al., 2012). As with the normal population, CVD can also be treated in CKD patients, representing a potentially preventable disease group. In 1998, the National Kidney Foundation (NKF) reported that CKD patients are a high-risk group for CVD. That report stated that a high prevalence of CVD had been determined in CKD patients, leading to mortality 10-30 times greater in the dialysis patient group in particular compared to the normal population. (Levey et al., 1998; Sarnak et al., 2003). Kidney function disorder is therefore a traditional risk factor held responsible in the development of CVD.

CVD risk factors in chronic kidney patients are divided into traditional and non-traditional (Sarnak et al., 2003). Traditional and non-traditional risk factors are given in the table. The main traditional risk factors are advanced age, diabetes mellitus, kidney disease, hypertension, family history, cigarette use, male gender, obesity, left ventricular hypertrophy and a sedentary lifestyle (Anderson et al., 1991; Mallamaci et al., 2002). However, there are studies showing that of the traditional risk factors known to be correlated with mortality in the normal population, the relationship between the mortality and HT and Hyperlipidemia in HD patients do not linear (Sarnak &Levey, 2000). The correlation between mortality and HT and elevated total cholesterol in this patient group is U-shaped (Lowrie & Lew, 1990; Zager et al., 1998). For this and similar reasons, a large number of studies have shown that traditional risk factors are inadequate in determining CVD risk in CKD (Cheung et al., 2000; Longe-

necker et al., 2002; Sarnak et al., 2003). Other studies have therefore investigated whether other factors may influence the development of cardiovascular events in the CKD patient group, and non-traditional risk factors have been developed. Hyperhomocysteinemia is the main non-traditional risk factor thought to affect the development of CVD in CKD. Several clinical studies have shown elevated homocysteine levels in the HD patient group and that hyperhomocysteinemia increases cardiovascular mortality (Bostom et al., 1997; Mallamaci et al., 2002; Manns et al., 1999; Sirrs et al., 1999). It is generally accepted today that oxidative stress and a progressive atherosclerotic process are correlated with development of cardiovascular events. Studies have also shown that this correlation also applies in the HD patient group. Oxidative stress may therefore be regarded as a non-traditional risk factor in the HD patient group (Boaz et al., 1999; Boaz et al., 1999). Inflammation (a rise in CRP) has been shown to be correlated with cardiovascular events in healthy individuals in prospective studies (Ridker et al., 1997). Studies also exist showing this relationship in the HD patient group (Zimmermann et al., 1999). As shown in the table 1, uremia-associated factors (anemia, impaired calcium-phosphorus metabolism, fluid electrolyte metabolism imbalance and dyslipidemia) may be added to the non-traditional risk factors in the HD patient group. As shown, dyslipidemia appears among both the traditional and non-traditional risk factors in the HD patient group. The reason is that, in contrast to the normal population, there are various lipid metabolism abnormalities in uremic patients and their being referred to as uremic dyslipidemia.

Traditional Risk Factors	Nontraditional Risk Factors
Advanced age	Hyperhomocysteinemia
Diabetes mellitus	Oxidative stress
Kidney disease	Inflammation
Hypertension	Anemia
Family history	Impaired calcium-phosphorus metabolism
Cigarette use	Fluid electrolyte metabolism imbalance
Male gender	Malnutrition
Obesity	Altered nitric oxide/endothelin balance
Left ventricular hypertrophy	Elevated fibrinogen level
Sedentary lifestyle	Other thrombogenic factors
Dyslipidemia (Higher LDL cholesterol, Lower HDL cholesterol)	Dyslipidemia
Family history of CVD	

Table 1. Traditional and Nontraditional Cardiovascular Risk Factors in Hemodialysis Patients

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3. Uremic dyslipidemia

Severe lipid metabolism disorders arise in patients with kidney failure, and the lipid metabolism disorder peculiar to this patient group is known as uremic dyslipidemia (Tsimihodimos et al., 2011). However, both the pathogenesis of uremic dyslipidemia and its relationship with the atherosclerotic process that leads to the development of cardiovascular events are debatable. Studies have shown that there is abnormality in all lipoprotein fractions in uremic patients. Factors influencing these abnormalities include the degree of kidney function impairment, primary disease, presence of nephrotic syndrome, whether renal replacement therapy is administered, and if so whether HD or peritoneal dialysis (PD), drugs used (antihyperlipidemic drugs, sevelamer, calcineurin inhibitors, steroid, etc.), and the presence of malnutrition and inflammation (Attman et al., 2011; Kaysen 2009; Tsimihodimos et al., 2008; Tsimihodimos et al., 2011; Vaziri and Moradi., 2006). Abnormality in lipid metabolism commences in the early stages of CKD and contributes to the development of cardiovascular complications by initiating the atherosclerotic process. Factors contributing to lipid metabolism in stage 1-4 CKD are known to include type of primary kidney disease, degree of proteinuria and use of drugs affecting lipid metabolism. The main lipid metabolism abnormalities seen in renal patients in these stages are hypertriglyceridemia, a rise in triglyceride remnant-rich lipoproteins and lipoprotein a (Lp (a)) levels, and a decline in HDL-cholesterol levels. Moreover, with the exception of nephrotic syndrome, Total (T) cholesterol and LDL-cholesterol levels are generally at normal limits in stage 1-4 CKD patients (Tsimihodimos et al., 2008; Vaziri & Moradi., 2006; Vaziri, 2006) A rise in LDL-cholesterol levels has been determined in patients with nephrotic syndrome (Tsimihodimos et al., 2008; Vaziri, 2006).

4. Dyslipidemia in hemodialysis patients

Before discussing specific lipid metabolism disorders in HD patients, some general information about lipid metabolism will assist understanding of dyslipidemia in this patient group.

Lipids are transported in plasma by means of water-soluble molecules known as lipoproteins. In addition to their transport characteristics, various enzymes in the lipid metabolism also serve as chemical reaction platforms converting transported lipids into one another. Lipoproteins possess a core consisting of non-polar lipids such as triglyceride and cholesterol and a surrounding structure consisting of polar lipids such as apolipoprotein and phospholipid. Thanks to the structural and catalytic functions of apolipoproteins in the structure of lipoprotein, by interacting with one another or various receptors they permit specific lipid species to be added to or removed from this lipoprotein. The main plasma lipoproteins are known as HDL, LDL, IDL and VLDL, depending on their functions and molecular structures (Dominiczak&Caslake., 2011; Vaziri, 2006).

Various changes take place in uremic dyslipidemia with the start of HD therapy. However, the lipoprotein and apolipoprotein profile in HD patients resembles that in pre-dialysis patients (Attman et al., 1993). The main lipid abnormality in this patient group is a rise in tri-

glyceride and triglyceride-rich remnant lipoprotein levels. Other lipid abnormalities are a rise in Lp (a) levels and a decrease in HDL. LDL levels are generally within normal limits. However, as with other lipoproteins, LDL is not homogeneous and there are variations in size, density and composition (Tsimihodimos et al., 2008; Wiemer et al., 2002).

Studies have shown that HD therapy has various effects on lipid profile. This gives rise to various differences, even though pathogenesis and lipid profile phenotype in HD patients are similar to the pre-dialysis period. One factor associated with HD therapy is membrane type. In one study, six weeks after transition from low flux membrane to high flux membrane, Blankestijn et al. observed a decrease in triglyceride and VLDL levels and an increase in HDL levels (Blankestijn et al., 1995). Docci et al. showed that polysulfone membranes have a more positive effect on lipid profile compared to cuprophan membranes (Docci et al., 1995). There are also studies showing that high flux polysulfone membranes reduce oxidized LDL (Wanner et al., 2004). Schiffl and Lang analyzed the effect of dialysate purity on dyslipidemia. They showed that ultrapure dialysis fluids brought about an improvement in dyslipidemia (Schiffl & Lang, 2010). Apart from dialysate purity, the effects of acetate or bicarbonate use on lipid profile have also been evaluated. It has been shown that use of bicarbonate dialysate can have positive effects on lipid profile (Jung et al., 1995). Another parameter thought to affect lipid profile during HD is heparin use. Heparin is known to cause lipoprotein lipase to be released from the endothelial surface. Chronic heparin use therefore leads to a decrease in lipoprotein lipase. Lipoprotein lipase is known to serve in the catabolism of triglyceride-rich lipoproteins such as chylomicrons and VLDL. The decrease in lipoprotein lipase in chronic heparin use gives rise to impairment in triglyceride-rich lipoprotein catabolism (Tsimihodimos et al., 2008). Studies analyzing the effect of unfractionated (UF) heparin on lipoprotein metabolism have produced controversial results. Mahmood et al. reported that heparin use during HD has no effect on lipoprotein lipase levels (Mahmood et al., 2010). However, there are also studies reporting that use of heparin has negative effects on both lipoprotein lipase and on lipid parameters (Daubresse et al., 1976; Schrader et al., 1990; Shoji et al., 1992). Another contentious issue is whether there is a difference in the use of unfractionated (UF) heparin and low molecular weight heparin (LMWH) in the effect on lipid parameters. Leu et al. determined a significant fall in T. cholesterol, LDL and Apo B levels after a transition from UF heparin to LMWH in hyperlipidemic HD patients (Leu et al., 1998). Yang et al., on the other hand, showed that the use of LMWH in diabetic hyperlipidemic HD patients caused a decrease in triglyceride and VLDL levels (Yang et al., 1998). Wiemer et al. showed that the use of LMWH brought about a decrease in oxidized LDL and triglyceride levels (Weimer et al., 2002). However, in an evaluation of the effects on lipid parameters of type of HD membrane and heparin type used, Katopodis et al. showed that both membrane and type of heparin have no effect on lipid parameters (Katopodis et al., 2004). Today, the effect of both heparin use and type of heparin on lipid parameters is debatable. We think that there is a need for studies analyzing the effect of HD therapy on lipoprotein metabolism in the HD patient group.

4.1. Triglyceride and triglyceride-rich lipoprotein metabolism disorders

As previously mentioned, hypertriglyceridemia is the most commonly seen lipid abnormality in both pre-dialysis and dialysis patients. Triglyceride-rich lipoprotein metabolism disorders give rise to an increase in triglyceride in CKD patients. The main triglyceride-rich lipoproteins are chylomicron and VLDL. Chylomicron and VLDL transport cholesterol from the intestine and liver to regions where it will be stored (adipose tissue) or used for energy (muscle cells). However, in order for chylomicron and VLDL to be able to do this they are exposed to various maturation processes. One of these is taking Apo E from HDL 2. Apo E enables binding to lipoprotein lipase and VLDL receptors. Another maturation process is taking Apo C-II from HDL 2. Apo C-II is a lipoprotein lipase activator. Apo C-III is a lipoprotein lipase inhibitor. Lipoprotein lipase enables the hydrolysis of chylomicron and VLDL and the fatty acids in them to be used by tissues (Tsimihodimos et al., 2011; Vaziri & Moradi., 2006; Vaziri, 2006). Through lipoprotein lipase, VLDL leads to a 70% decrease in hydrolyzed triglyceride content and the formation of remnant VLDL (IDL). IDL transfers Apo E and Apo C-II in plasma to HDL. After the transfer of the remaining triglycerides to HDL through the mediation of cholesteryl ester transfer protein (CETP), they are lipolyzed through mediation of hepatic triglyceride lipase.

Triglyceride metabolism defects emerge because of a rise in synthesis and/or a decrease in clearance. Lipoprotein lipase is very important in triglyceride and triglyceride-rich lipoprotein clearance. Vaziri et al. showed a decrease in lipoprotein lipase gene expression in several tissues in uremic patients (Vaziri & Moradi., 2006). There may be several causes of a decrease in lipoprotein lipase levels and efficacy in HD patients. One is the heparin use discussed in detail above (Daubresse et al., 1976; Schrader et al., 1990; Shoji et al., 1992). UF heparin use leads to a decline in lipoprotein lipase levels. Another cause is a reduced lipoprotein lipase activator (Apo C-II) and inhibitor (Apo C-III) ratio in HD patients (Chan et al., 2009; Moberly et al., 1999). Studies have shown that impaired Ca-P metabolism and secondary hyperparathyroid lead to a decrease in lipoprotein lipase activity (Akmal et al., 1990; Vaziri et al., 1997). In addition, physical inactivity, insulin resistance and an abnormal T4 (thyroxin) to-tri-iodothyromin (T3) conversion contribute to a decrease in lipoprotein lipase activity (Vaziri & Moradi., 2006). Another cause of reduced clearance is a decrease in hepatic lipase activity. Studies have shown a decrease in hepatic lipase activity in uremic patients. A decrease in hepatic lipase activity causes a decrease in the clearance of chylomicron remnants and IDL and a rise in plasma levels (Klin et al., 1996). Down regulation of VLDL receptor in various tissues is one cause of increased VLDL in plasma (Vaziri & Liang., 1997). Apart from decreased clearance, a rise in synthesis from the liver also contributes to hypertriglyceridemia. Insulin resistance is thought to be one of the factors leading to hypertriglyceridemia in HD patients by increasing hepatic VLDL production (Tsimihodimos et al., 2011). Another reason for increased triglyceride synthesis is the use of acetate dialysate, even though this is not used today. The acetate in the dialysate represents the source for fatty acid synthesis by passing into the blood (Vaziri, 2006). In addition to the use of heparin in HD therapy, various therapy-related factors are thought to cause modifications in triglyceride and triglyceride-rich lipoproteins. Use of a high flux membrane has been shown to re-

duce triglyceride levels in some studies, and to have no effect in others (Ottosson et al., 2001; Wanner et al., 2004).

4.2. High density lipoprotein metabolism impairment

Another frequently seen impairment of lipid metabolism in the CKD patient group, which includes HD patients, is a reduction in HDL cholesterol and impaired HDL metabolism. Impairments in HDL metabolism appear in the form of decreased Apo AI, impaired HDL maturation, increased HDL triglyceride and a rise in plasma pre β HDL (Pahl et al., 2009; Quaschning et al., 2001; Vaziri, 2006). The main function of HDL is to collect excess cholesterol from peripheral tissues and transport it to be metabolized in the liver (Genest et al., 1999). In addition, the fact that HDL levels decrease as a response to information suggests that it has an inhibitor effect on inflammation (Quaschning et al., 2001; Vaziri 2006). This inhibitor effect also occurs on platelet adhesion and LDL oxidation (Navab et al., 2001). As previously mentioned, another function of HDL is to represent a source for Apo CII and Apo E, which occupy an important place in the metabolism of triglyceride-rich lipoprotein. The most important proteins in the structure of HDL are Apo AI and Apo AII. Apo AI is an activator of lecithin cholesterol acyl transferase (LCAT), which occupies an important place in HDL metabolism. LCAT performs an important function in HDL maturation and in the mediated uptake of HDL from the peripheral tissue to be metabolized in the liver (Kaysen, 2009; Guarnieri et al., 1978; McLeod et al., 1984). Apo AII is a hepatic lipase activator permitting the metabolism of HDL-origin triglyceride (Vaziri, 2006). Okuboet al. showed that the level of Apo AI and Apo AII is low in uremic patients, and that the fall in Apo AI is related to a rise in catabolism and the fall in Apo AII to a decrease in production (Okubo et al., 2004). Low levels of Apo AI and Apo AII are one of the causes of low HDL in HD patients (Attman et al., 2011; Attman et al., 1993) Another reason for lowered HDL and impairment in its metabolism is LCAT deficiency (Guarnieri et al., 1978; Kaysen 2009; McLeod et al., 1984). A decrease in hepatic lipase activity in uremic patients has already been discussed. The role of hepatic lipase in the metabolism of HDL is to assist the hydrolysis and removal of HDL triglyceride content. When it is deficient, a rise in HDL triglyceride takes place (Klin et al., 1996). Cholesterol ester transfer protein (CETP) takes triglycerides by transferring cholesterol esters from HDL to LDL (Davidson and Toth, 2007; Madeleine et al., 2009; Vaziri, 2006). Kimura et al. showed a high CTEP level in HD patients (Kimura et al., 2003). Elevated CTEP may cause a rise in HDL triglyceride in this patient group (Vaziri, 2006). Studies have shown that the HD procedure itself has an effect on HDL-cholesterol levels in HD patients. One such study was performed by Jung et al. Those authors evaluated the effect of citrate and bicarbonate dialysate use on HDL-cholesterol levels and showed that bicarbonate dialysate use increased HDL-cholesterol levels (Jung et al., 1995). Another parameter affecting HDL-cholesterol level is the use of a low flux or high flux dialyzer. Studies have shown that use of a high flux membrane increased Apo AI and HDL-cholesterol levels (Blankestijn et al., 1995; Docci et al., 1995). In conclusion, with both its relation with CKD and the effect of HD therapy, the level of HDL-cholesterol, which has antiatherogenic, anti-inflammatory and antiplatelet functions, declines in the HD patient group, and various impairments arise in the metabolism.

4.3. Low density lipoprotein (LDL) and cholesterol metabolism impairment

LDL is the major source of extracellular cholesterol. In HD patients, as with CKD patients without pre-dialysis proteinuria, cholesterol and LDL levels are normal or low (Kharrat et al., 2012; Shoji et al., 1992; Vaziri, 2006). Although the LDL level is normal or low, the level of small dense LDL with its atherogenic potential is high (Alabakovska et al., 2002; Kaysen, 2009). Additionally, there is an increase in oxidized LDL, thought to be correlated with atherogenic and cardiovascular mortality. As shown in several previous studies, Mahrooz et al. demonstrated high oxidized LDL levels in HD patients (Mahrooz et al., 2012, Samouilidou et al., 2012). However, the findings from studies regarding the relation between oxidized LDL levels and mortality and morbidity are controversial. Asamiya et al. showed that the oxidized LDL/LDL-cholesterol ratio is higher in patients with coronary artery calcification (Asamiya et al., 2012). Sevinç ok et al. reported that neither oxidized LDL nor non-oxidized LDL values are correlated with mortality (Sevinc ok et al., 2012). Pawlak et al. reported low oxidized LDL in HD patients but high antibodies against oxidized LDL, and that the oxidized LDL/oxidized LDL antibody ratio might be a new marker for cardiovascular events (Pawlak et al., 2012). Mention has already been made of studies showing that LDL is small and dense in HD patients. Noori et al. determined no correlation between conventional lipid parameters and mortality, but showed that very small LDL particle concentration is correlated with mortality (Noori et al., 2011). Kimura et al. showed that small size LDL is correlated with coronary artery disease (Kimura et al., 2011). In conclusion, LDL levels are normal or low in the HD patient group while LDL fractions (oxidized LDL, small dense LDL) with their atherogenic potential are higher in this patient group.

4.4. Lipoprotein(a) metabolism impairment

Lipoprotein (a) (Lp (a)) is a LDL-like particle. It is distinguished from LDL by the presence of apolipoprotein (a) (Apo (a)). Apo a binds to Apo B-100 with disulfide bonds. Because of Apo (a)'s similarity to plasminogen it is thought to contribute to thrombogenesis by inhibiting fibrinolysis of Lp (a) (Milionis et al., 1999; Tsimihodimos et al., 2011). There have been many studies regarding the correlation between elevated Lp (a) and cardiovascular events in the normal population (Rader &Brewer., 1992; Schaefer et al., 1994). There have also been several studies on the subject in HD patients, with high levels being shown in these (Dieplinger et al., 1993; Hirata et al., 1993; Kronenberg et al., 1995). Several clinical studies have evaluated the relation between Apo (a) size and Lp (a) level. Correlations have been determined between Apo (a) low molecular-weight (LMW) isoforms and elevated Lp (a) levels, and also between high-molecular-weight (HMW) isoforms and low Lp (a) levels (Boerwinkle et al., 1992; Kraft et al., 1992). The relationship between Apo (a) phenotype and elevated Lp (a) in HD patients is questionable (Hirata et al., 1993; Kronenberg et al., 1995). One of these studies, by Milionis et al., determined elevated Lp (a) and Apo (a) levels in HD patients (Milionis et al., 1999). Kronenberg et al.'s study supported these findings (Kronenberg et al., 1995). However, Kronenberg et al.'s 1999 study showed that LMW Apo (a) phenotype is an independent predictor for CAD (Kronenberg et al., 1999). The Choices for Healthy Outcomes in Caring for ESRD (CHOICE) study showed that Lp (a) levels are high in young,

white patients and correlated with cardiovascular events. However, that study also stated that Apo (a) size is not correlated with elevated Lp (a) and cardiovascular events (Longenecker et al., 2002). In conclusion, while the correlation between elevated Lp (a) and Apo (a) size in the HD patient group is still unclear, elevated Lp (a) in particular is thought to be a cardiovascular risk factor.

4.5. Reverse epidemiology in hemodialysis patients

Hyperlipidemia is known to be one of the most important cardiovascular risk factors in the normal population (Gordon et al., 1977). However, the relationship between dyslipidemia and mortality in HD patients is controversial. Cheung et al. determined that several traditional risk factors, including T. cholesterol, were not correlated with mortality in HD patients (Cheung et al., 2000). A cross-sectional study by Stack et al. produced similar results (Stack & Bloembergen). However, some studies have reported a correlation between dyslipidemia and mortality (Hahn et al., 1983; Nishizawa et al., 2003). As already discussed, whether renal replacement is performed with CRD patients, and whether that replacement is HD, modifies lipid metabolism disorders. No dyslipidemia-mortality correlation has been determined in certain patient populations (cancer patients, hospitalized patients, etc.) including the HD patient group (Shoji et al., 2011). This reverse relationship is therefore known as 'reverse epidemiology' (Kalantar-Zadeh et al., 2004). Hypercholesterolemia, high body mass index (BMI) and hyperhomocysteinemia lead to shortening in long-term survey in the normal population. But in the HD patient these factors lead to an increase in short-term survey. Researchers have described this to malnutrition inflammation (MIA) syndrome (Stenvinkel et al., 1999). MIA syndrome is known to be correlated with atherosclerosis and mortality in HD patients. Presence of hypercholesterolemia, high BMI and hyperhomocysteinemia in this patient group shows that nutrition status may be good. Improvement in MIA in these patients may cause a decrease in mortality (Nurmohamed &Nubé, 2005). In conclusion, these traditional risk factors for HD patients should be reviewed and new treatment objectives set out.

4.6. Treatment

It is today recognized that there is a correlation between hyperlipidemia and cardiovascular events in individuals with normal renal functions and that cardiovascular mortality can be reduced by treating hyperlipidemia. It has been shown in several randomized, controlled meta-analyses that reducing LDL cholesterol with statin therapy brings about a significant decrease in CAD and myocardial infarction (MI) in the normal population (Baigent et al., 2005). However, in the same way that impairments in lipid metabolism in HD patients differ from those in individuals with normal renal functions, so there are various differences in dyslipidemia treatment in these patients. This section discusses dyslipidemia treatment and its effect on mortality and morbidity in the light of major studies.

4.6.1. The use of statin in dyslipidemia treatment

The use of statin has been shown to have a lowering effect on mortality and morbidity in hyperlipidemic patients without renal function disorder. Statin use in pre-dialysis CKD patients is known, with its LDL-cholesterol reducing effect and an effect independent of the lipid lowering effect known as pleotropic effect, to reduce mortality and morbidity and to slow renal progression (Deshmukh & Mehta., 2011; Olyaei et al., 2011). Statins' pleotropic effects may be listed as a decrease in endothelial cells' permeability to LDL, an increase in vasodilator response, a decrease in endothelial adhesion molecules and an antioxidant effect (Vaughan et al., 2000). The use of statin in HD patients is controversial. One study on the subject by Saltissi et al. showed that simvastatin significantly reduces non-HDL cholesterol levels (Saltissi et al., 2002). Chang et al. determined that simvastatin has an anti-inflammatory effect as well as a lipid-reducing one in HD patients (Chang et al., 2002). These and similar studies have shown that statins have a lipid-reducing effect in HD patients, as well as the presence of pleotropic effects (Nishikawa et al., 1999; Soliemani et al., 2011; van den Akker et al., 2003). One piece of research to investigate the effect on mortality of statin therapy was the Deutsche Diabetes-Dialyse-Studie (4D) study. This was a prospective, randomized study involving 178 HD centers. It included more than 1000 diabetic HD patients and observed 21% MI -associated mortality in the group receiving atorvastatin and the control group. However, sudden cardiac death-related cardiac mortality levels approaching 50% developed in both groups. The researchers suggested that sudden cardiac deaths might be related to arrhythmia and were not reduced by the use of statin (Wanner et al., 2005). Another major piece of research, the AURORA study published in 2009, included 2776 HD patients. That study showed that despite a significant fall in LDL cholesterol with rosuvastatin, there was no significant decrease in cardiovascular mortality (Fellström et al., 2009). Finally, the SHARP study was conducted with 9270 patients with CKD (3023 dialysis patients). In that study, simvastatin + ezetimibe (4193 simvastatin plus ezetimibe from the start, 457 beginning with simvastatin alone and then plus ezetimibe after one year) was administered to one arm, and placebo (4191 plus at the beginning, 429 plus one year after) to the other. Average duration of monitoring was 4.9 years. Major cardiovascular events (non-fatal myocardial infarction or coronary death, non-hemorrhagic stroke, or arterial revascularization) were observed in 11.3% of the simvastatin plus ezetimibe group, and in 13.4% of the placebo group. A 17% fall in major atherosclerotic events was observed with a decrease of 0.85 mmol/L in LDL. In addition, this decrease in risk did not alter depending on whether the patients enrolled received dialysis therapy or not. In other words, in contrast to the 4D and AURORA studies, a decrease in major cardiovascular events was brought about with statin therapy in that study (Baigent et al., 2011).

4.6.2. The use of ezetimibe in the treatment of dyslipidemia

Ezetimibe is a selective intestinal cholesterol absorption inhibitor. Prevention of cholesterol absorption in addition to inhibition of cholesterol synthesis has been shown to reduce cardiovascular mortality in recent years. For that reason, studies have begun being performed regarding the use of ezetimibe alone in patients with a high risk of side-effects from ezetimibe

plus low-dose statin combinations or statin for the purpose of reducing side-effects frequently observed with statins, particularly at increased doses (myopathy/myositis, hepatitis, etc.). In the HD patient group, in which the effect of statin on mortality and morbidity is controversial, studies with low patient numbers have shown that ezetimibe produces a reliable and effective fall in cholesterol (Hattori & Hattori., 2010; Ahmed & Khalil., 2010). Finally, the SHARP study showed that simvastatin plus ezetimibe produced a significant decrease in atherosclerotic cardiovascular events (Baigent et al., 2011).

4.6.3. The use of fibrate in the treatment of dyslipidemia

Fibrates have been used for many years, particularly in the treatment of hypertriglyceridemia. In the HD patient group, hypertriglyceridemia exhibits a pronounced impairment of lipid metabolism. HD would therefore seem to represent a potential patient group for fibrate use. However, since fibrate metabolites are eliminated by the kidney, and since these metabolites give rise to serious side-effects such as myopathy and rhabdomyolysis by accumulating with a decrease in glomerular filtration rate, use in this patient group is limited. However, one study including some 9000 patients published in 2012 showed that fibrate use is quite safe and effective in diabetic patients with moderate renal damage. Patients with a GFR above 30 were included in that study, however (Ting et al., 2012). There are not many studies concerning the use of fibrate in HD patients. One such study is that by Makówka et al. The study included 27 chronic HD patients and lasted for 63 days. It determined a significant fall in T cholesterol, LDL and triglyceride with fenofibrate therapy and a significant rise in HDL. AST and ALT levels remained normal in patients receiving fenofibrate, while CPK levels rose significantly compared to basal values but then remained stable (Makówka et al., 2012). Prospective randomized studies involving large patient numbers evaluating the reliability and efficacy of fibrate use in the HD patient group are now needed.

4.6.4. Use of nicotinic acid in the treatment of dyslipidemia

Nicotinic acid is a water-soluble vitamin B complex (vitamin B3) that has been used in the treatment of hypertriglyceridemia for many years. It produces a fall in triglyceride, LDL and VLDL levels and a rise in HDL. However, hepatoxicity and flushing are side-effects that limit its use. While there have been pharmacokinetic studies in HD patients, studies showing its effectiveness in the treatment of dyslipidemia are restricted to a very small number of cases (Reiche et al., 2011). There are no studies showing its effect on mortality and morbidity. Restrepo Valencia and Cruz reported a fall in T. cholesterol and triglyceride levels and a rise in HDL after nicotinic acid therapy in 3 HD and 6 PD patients (Restrepo Valencia &Cruz., 2008). Shahbazian et al. reported a rise in HDL cholesterol in 48 HD patients after 8-week nicotinamide therapy (Shahbazian et al., 2011).

4.6.5. The use of sevelamer in the treatment of dyslipidemia

Sevelamer hydrochloride is a non-calcium containing phosphorus-binding resin used in the treatment of hyperphosphatemia in HD patients. The Dialysis Clinical Outcomes Revisited (DCOR) and Renagel in New Dialysis (RIND) studies showed that it provides a better sur-

vey that calcium-containing phosphorus-binders (Block et al., 2007; Suki et al., 2007). Sevelamer prevents the absorption of intestinal cholesterol. Studies have shown it has positive effects on lipid parameters in HD patients (Yamada et al., 2005; Qunibi, 2005). Iimori et al. showed that dyslipidemia improved significantly with treatment with sevelamer and that mortality declined (Iimori et al., 2012). However, the use of sevelamer in the treatment of dyslipidemia in HD patients has not been accepted due to the lack of wide-ranging and long-term studies.

4.6.6. The use of carnitine in the treatment of dyslipidemia

Also known as trimethyl-aminobutyric acid, carnitine is a naturally-occurring vitamin-like substance. Carnitine serves in several important metabolic pathways. One of the most important of these is that it lowers the level of free fatty acid necessary for triglyceride synthesis and beta-oxidation of fatty acids (Guarnieri et al., 2001). Since the kidneys are an important site of carnitine synthesis, that synthesis decreases in the event of kidney failure (Bellinghieri et al., 2003). Studies exist showing that carnitine therapy has a positive effect on lipid parameters in HD patients, while others report no positive effect (Emami Naini et al., 2012; Naini et al., 2012; Hurot et al., 2002; Guarnieri et al., 2007). For that reason, carnitine is not definitively accepted in the treatment of dyslipidemia in HD patients.

4.6.7. Heparin-induced extracorporeal LDL precipitation

Heparin-induced extracorporeal LDL precipitation (HELP) is a form of lipid apheresis particularly used in the treatment of familial hyperlipidemia. The number of case reports in the literature is limited, although a significant lipid decrease has been observed with HELP. One of this limited number of studies in the literature is that by Bosch et al. A pronounced fall in LDL was observed with 29 sessions of HELP in 5 HD patients (Bosch et al., 1993). Another study by Bosch et al. reported quite good results with HELP in 3 HD patients (Bosch et al., 1993). Eisenhauer et al. achieved a significant fall in LDL cholesterol with HELP in 6 HD patients (Eisenhauer et al., 1991). In the light of these case reports, we think that HELP may be a useful form of treatment, especially in HD patients with familial hyperlipidemia and with no response to drug therapy.

4.6.8. Guideline

The K-DOQI treatment of hyperlipidemia guideline was published in 2003 because of the variation in dyslipidemia in HD patients (Kidney Disease Outcomes Quality Initiative (K/DOQI) Group, 2003) Until then, there had been recommendations resembling an adult hyperlipidemia guideline in the studies performed. In essence, the recommendations of that guideline are as follows;

In order to prevent serious complications such as pancreatitis in patients with a triglyceride level above 500 mg/dl, primary focus must be on triglyceride-lowering therapy. Diet, fibrate and nicotinic acid can be used in treatment.

If the triglyceride level is below 500 mg, treatment should be adjusted according to LDL levels. If LDL is above 100 mg/dl, LDL-lowering therapy (diet and statin) is recommended.

If LDL is normal while triglyceride is elevated, there is generally a rise associated with lipid remnants. The amount of remnant lipoprotein can generally be estimated with a calculation of non-HDL cholesterol. Non- HDL cholesterol is calculated as the difference between T. cholesterol and HDL cholesterol. Treatment is recommended in patients with non-HDL cholesterol above 130 mg/dl.

As already stated, because of the insufficient number of studies, the dyslipidemia treatment guideline in chronic kidney patients was adapted to the adult hyperlipidemia treatment guideline. However, it is clear that treatment in HD patients requires a different approach. We therefore think that this guideline published in 2003 should be updated in the light of more recent studies.

5. Conclusion and recommendations

The pathogenesis of dyslipidemia in the HD patient group, which has various impairments in lipid metabolism, has not yet been fully clarified. New studies regarding that pathogenesis are therefore needed. In addition, new studies regarding what the aim of treatment in dyslipidemia and the parameter to be targeted should be (triglyceride, LDL, IDL, VLDL or non-HDL cholesterol?). Finally, treatment adapted to the adult hyperlipidemia treatment guideline because of a lack of sufficient studies must clearly be turned into a lipid guideline aimed at HD patients in the light of newly published studies.

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