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Department of Surgery and Transplantology, Medical University of Lublin

KRZYSZTOF JANICKI, GRZEGORZ MOLAS,
JACEK FURMAGA, STANISŁAW PIEPRZNY,
JANUSZ GIERYNG, MICHAŁ KUFEL, SŁAWOMIR RUDZKI

Abnormal lipoprotein metabolism in hemodialysis patients

Chronic renal patients and those treated with hemodialysis are among those particularly exposed to accelerated artherosclerosis resulting in cardiovascular disease which ends up in death in 40–50% of patients (2). These patients are 10–20% as likely to develop myocardial ischaemia or infarction (4).

With these data, a thorough assessment of risk factors for development of artherosclerosis and cardiovascular disease as well as an attempt to eliminate them appear of utmost importance.

Risk factors for artherosclerosis in chronic renal patients can be divided into general (classic) and uremia-related. The latter include proteinuria, intracellular overhydration, electrolyte metabolism disturbance, anemia, elevated concentration of triglycerides, llipoprotein (a) and homocysteina, clotting disturbances, oxidation stress, non- specific inflammatory process and urenic toxins (10, 11).

It should be stressed that most of above mentioned risk factors are connected with the endothelial disfunction which is a link between risk factors and cardiovascular disease.

Moreover, endothelial disfunction affects considerably lipoprotein metabolism, particularly hypertriglycerinemia. It has also been reported that elevated concentration of chylomicrons and remnants occurring before and after meals in dialysis patients results from endothelial disfunction.

Dislipidemia, which occurs in chronic renal failure and hemodialysis patients manifests itself by elevated concentration of TG, VLDL, LDL, JDL as well as a decrease in HDL-C cholesterol level. Peritoneal dialysis patients show slightly increased TC level, whereas those treated with hemodialysis have it either correct or even a bit decreased (9).

A rise in Lp (a) concentration has also been noted (8, 12). Dialysis therapy may even enhance this process.

Mechanisms leading to elevated TG concentration in dialysis patients are the following: enhanced TG synthesis in liver from free fatty acids released from fatty tissue and muscles, and impairment of lipoprotein metabolism due to decreased activity of enzymes involved in it, that is lipoprotein lipose (LPL), lecithin-cholesterol acetyltransferase (LCAT), hepatic triglycerin lipase (HTGL).

Abnormalities in enzyme activity are caused by their impaired synthesis as well as by the deficiency of activators and an increasing number of the inhibitors or these enzymes. Their activity is additionally inhibited by TNF-α, 1 (IL-1) interleukin, 2 (IL-2) interleukin and 6 (IL-6) interleukin, which mediate inflammatory process. Dialysis patients show synthesis and concentration growth in the serum of those cytokines, and an elevated level of C reactive protein (CRP). Those data support the idea that the inflammatory procces may be partly responsible for lipoprotein metabolism abnormalities in dialysis patients (3, 11).

Our studies revealed that hemodialysis and renal transplant patients show considerably higher level of ApO C III which curbs lipoprotein lipase (6).

LPL activity drop results in the inhibition of TG hydrolysis – a reaction catalysed by this enzyme. However lower activity of LCAT hampers cholesterol estrification which is additionally impaired due to smaller LDL cholesterol fraction. A prolonged hyperglycemia occurring after meals rich in carbohydrates enhances TG synthesis in dialysis patients. Hyperglycemia enables transfer of bigger than usual amount of glucose into hepatocytes and so they contain more substrate from which TG can be synthetized. In peritoneal dialysis patients, dialysis fluid, rich of glucose, is an additional source of this sugar. Still another important factor enhancing TG synthesis in liver is excessive lipolysis of fatty tissue due to impairment of antilipatic insulin activity and increased activity of lipolysis stimulating factors such as glucagons, growth hormone and glycocorticosteroids whose number in the patients serum increases. As a consequence, a lot of free fatty acids are released and even transferred by blood to liver where they become substrate for TG synthesis. On the other hand, deficiency of carnitine, a compound playing a significant role in lipid tissue metabolism, contributes to the inhibition of TG degradation in dialysis patients. It should be stressed that increased TG synthesis in dialysis patients is a combined effect of many different factors.

Prinsen et al published in Kidney Int. 2033 a simple diagram showing different mechanisms leading to triglyceridemia in patients with chronic renal failure (14).

Lower cholesterol concentration in HDL fraction is, besides hypertriglyceridemia, another alternation relating to lipoprotein profile in dialysis patients.

Apo A I and Apo A II are the main apoproteins included in HDL. HDL is considered important for the role it plays in transforming cholesterol from tissues and vascular walls back to the liver. This so-called "reverse cholesterol transfer" from tissues to liver is a part of HDL-2-HDL-3-HDL-2 transformation process in which LPL and HGL enzymes as well as proteins transporting lipids are present. Fall in enzyme activity in dialysis patients impairs the reverse cholesterol transfer. Antitherogenic properties of HDL are responsible for hampering the oxidative modification of LDL. Due to the presence of paraoxynase and vitamine E in HDL molecule, high HDL concentration prevents LDL oxidation in vascular walls and counters platelet aggregation by means of cyclooxygenase gene adjustment.

A drop in HDL concentration as well as hypertriglyceridemia make dialysis patients more vulnerable to myocardial ischemia and other cardiovascular problems (7).

Patients undergoing renal replacement therapy are also reported to have higher lipoprotein (a) [Lp (a)] concentration. Many scientists say it is an independent risk factor for myocardial ischemia.(13)

Our studies revealed high Lp (a) concentration in peritoneal dialysis (mean 0.36 g/L) and hemodialysis patients (mean 0.21 g/L) in comparison to control group (mean 0.09 g/L) (8).

Structural similarity between Apo (a) and plasminogen relates elevated concentration of Lp (a) to fibrynolysis disturbance. LP(a) and plasminogen fight each other to bond with the receptor for plasminogen and Lp(a) competes with tissular activator of plasminogen for bonding with fibrine, which in turn hampers the process of plasmin formation. Lp(a) is a link between atheromatous and thrombatic processes.

Some authors point to the role of receptor abnormalities in lipoprotein metabolism. They can, among other things, lead to the accumulation of oxidated LDL molecules which promote atheromatous process. There are not many papers on apolipoprotein disturbances in dialysis patients (1).

In these patients disapoproteinemia is reported to develop prior to and be more intensified than dyslipidemia. Our studies showed a decline in Apo A I concentration and rise in Apo B, Apo C III, Apo E concentration both in hemodialysis and peritoneal dialysis patients. The same abnormalities

could be noticed in different apolipoprotein parameters, which suggests that the structure of the molecules has been disturbed (5, 6).

Hypertrigliceridemia and HDL cholesterol drop in dialysis patients are rated among high risk factors for cardiovascular complications, according to the European Cardiological Society. In most dialysis patients the disturbance of lipid matabolism is so serious that they need to be put on a special diet or administered some medications of which statines are most often used (15), although fibrates turn out to be more effective in renal replacement patients. Fibrates and their therapeutic properties have been presented in the table (Tab. 1).

Table 1. Fibrates and their function

Reducing trigliceryde concentration in blood serum by 20–25%
Reducing total cholesterol concentration
HDL – cholesterol rise by 10–15%
Regulating postprandial lipemia
Poor results in reducing LDL – cholesterol – only by 10–15% (phenofibrate micronised and α cyprofibrate appear more effective)
Reducing beneficially small dense LDL pools

Thanks to molecular biology we know fibrates work and affect lipoprotein metabolism. They act on cellular level through PPAR receptors, particularly PPAR – after which are present in liver and convey stimuli onto the genes coding lipoprotein metabolism. These receptions enhance gene expression for lipoprotein lipase and at the same time inhibit Apo C III synthesis, which leads to triglyceride decline. The fibrates also contribute to eliminating LDL molecules and alternating their structure.

Unfortunately, fibrates are still not appreciated enough in clinical practice.

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SUMMARY

Patients with chronic renal failure and those treated with hemodialysis are particularly exposed to accelerated artherosclerosis which may cause cardiovascular diseases. The purpose of this study is to describe different risk factors contributing to the development of these diseases and to significant disorders in lipid and lipoprotein metabolism in particular. Referring to our studies and most often cited articles, we described various types of lipoprotein metabolism disfunctions. We have also compared major risk factors of lipoprotein metabolism. From all those data we conclude that pharmacological treatment (recommended drugs are fibrates and statines) is required in patients at risk.

Zaburzenia gospodarki lipoproteinowej u pacjentów leczonych nerkozastępczo

Chorzy na przewlekłą niewydolność nerek oraz pacjenci leczeni nerkozastępczo należą do grupy szczególnie zagrożonej rozwojem miażdżycy i wynikających w jej następstwie powikłań sercowo-naczyniowych. W pracy omówiono różne czynniki ryzyka prowadzące do wystąpienia takich powikłań, ze szczególnym uwzględnieniem zaburzeń gospodarki lipidowej i lipoproteinowej. W oparciu o dane z piśmiennictwa oraz badania własne opisano rodzaje zaburzeń gospodarki lipoproteinowej występujące u pacjentów leczonych nerkozastępczo. Zwrócono również uwagę na różne czynniki prowadzące do ich wystąpienia. W zależności od rodzaju zaburzeń gospodarki lipoproteinowej pacjenci wymagają leczenia farmakologicznego.