

LIPID PROFILE AND CONCENTRATION OF ApoA-1 AND ApoB-100 IN PATIENTS WITH END-STAGE RENAL DISEASE TREATED BY REPEATED HAEMODIALYSIS

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Abstract: Lipid metabolism disorders in patients with end-stage renal disease, particularly in patients with nephrotic syndrome, were described by Dr Bright as long ago as 1827 [1].

It is known that patients with end-stage renal disease (ESRD) display a clinical picture of early accelerated (premature) atherosclerosis with severe cardiovascular and cerebral complications that are very often present even at a relatively early age compared with the general population.

Today, it is considered that uraemic dyslipidaemia has persisted for many years before chronic dialysis treatment begins and presents a basic risk factor for an early start of the atherogenic processes. That is why an analysis of apolipoprotein and lipid abnormalities as well as their etiopathogenetic mechanism in patients diseased with ESRD treated with repeated haemodialysis in the initiation phase of dialysis (the first 6 months), can clearly contribute to taking timely preventive measures (dietetic, healing) by which the frequency of apolipoprotein and lipid abnormalities will be decreased, which, at the same time, will result in reducing the processes of early atherosclerosis with all its complications in ESRD patients [2].

Disorders of apolipoprotein metabolism are considered as one of the most important factors for early atherosclerosis in patients with ESRD [3].

Key words: Apolipoprotein A-1 (ApoA-1), Apolipoprotein B-100 (ApoB-100), End-Stage Renal Disease (ESRD), Lipid profile (Total cholesterol-TCh, Triglycerides-TG, HDL-cholesterol, LDL-cholesterol), Haemodialysis, Early atherosclerosis.

Introduction

A basic risk factor for early atherosclerosis in patients with end-stage renal disease (ESRD) treated by repeated haemodialysis is a disorder in the lipoprotein metabolism [15, 16, 17] which is described by a modified proportion of respective lipids and apoproteins in the composition of the lipoprotein (Lp) molecule (called dyslipidaemia [18, 19, 23, 30]. Genetic predictors for an early predisposition to atherosclerosis are disordered reverse transport of HDL-ch [31] and insufficient expression of B compared to E-receptors, as well as reduced conversion of VLDL in IDL and finally in LDL-ch [38].

Lipo/apoprotein aberrations in uraemia concerns all lipoprotein (Lps) particles.

Hypertriglyceridaemia predominates due to increased triglyceride content structure of VLDL, IDL, LDL-ch and HDL-ch. ApoA-1 is decreased in the structure of LDL-ch, while ApoA-IV has a greater incidence. The concentration of ApoB-100 is increased in the VLDL composition. Decreased concentrations of HDL-ch in patients on dialysis reduce the reverse cholesterol transport to the liver, which creates conditions for cell accumulation of cholesterol in extrahepatic tissues [33].

Patients with ESRD present a higher incidence of ApoB/E in the structure of total cholesterol, TG and LDL-ch compared with their presence in the composition of HDL-ch. A lower concentration of ApoA-1 and increased concentration of ApoB-100 was detected in all patients. Higher values of ApoB-100 and smaller concentrations of ApoA-1 were found in patients treated with CAPD in comparison with patients treated with chronic haemodialysis. Thus it can be concluded that various dialysis modalities have an influence on the lipoprotein metabolism and evolution of atherosclerotic disease in dialysis patients [34]. Decreased liver synthesis in ApoA-1 is the basic reason for its low plasma concentration in uraemic patients with a compensatory increased synthesis of ApoB-100.

Apolipoprotein A-1 is the dominant protein in the class of HDL (65%) that is synthesized in the liver and intestinal mucosa. ApoA-1 acts as an activator of LCAT, transports lipids and is a ligand for HDL-receptors.

Apolipoprotein B-100 dominates quantitatively in the class of LDL, VLDL, IDL, Lp (a) and in smaller measure in hilomikrones (HM). ApoB-100 is a ligand for the receptors (B, E) of LDL. It is synthesized in the liver. *The reference value is 0.5–1.60 g/l.*

The aim of the study was to determine the concentrations of ApoA-1, ApoB-100, their abnormalities and the lipid profile in patients with ESRD treated with repeated haemodialysis, as well as their role in the etiology of premature atherosclerosis in patients with ESRD treated with repeated haemodialysis.

Materials and methods

Patients' blood and blood of a control group of examinees was used for the investigations. The blood was drawn at 08 : 00 hours in the morning when the room temperature was from 19 to 24⁰C while the patients were in a lying position with the aim of avoiding all possible variations of values in separate lipoprotein fractions (from 9 to 12%) that appear when patients are in a standing position. The blood sample was taken immediately prior to the start of haemodialysis treatment (HD), after at least 12 hours of fasting in order to avoid the intestinal-absorption effect of food upon serum lipids (postprandial hypercholesterolaemia). Laboratory analyses were determined once a month by three consecutive measurements in all patients. The presented results actually represent a mean value of the three consecutive measurements under identical conditions. The obtained blood, preserved by several drops of heparin, was sent to the Medical Centre in Tetovo and to the Clinical Biochemistry Institute at the Clinical Centre in Skopje (in 3 ccm serum) in order to organize inspection and calibration of the exactness of the methods used.

The lipid profiles, ApoA-1 as well as ApoB-100, were analysed in 120 patients for several months at the Nephrology and Haemodialysis Department at the Medical Centre in Tetovo and at the Nephrology Clinic of the Medical Faculty in Skopje.

The division of patients according to the basic kidney disease is presented in Table 1.

Table 1 – Табела 1

Division of patients according to basic nephropathy
Поделба на пациентиите согласно основното заболување

<i>Patients total = 120</i>	Men = 66 (55%), Women = 54 (45%)
<i>Mean age (years)</i>	59.5 ± 12.8
<i>Glomerulopathies (GH)</i>	30 (25%)
<i>Arterial hypertension with sec. nephroangiosclerosis (HTA, NaS)</i>	28 (23.3%)
<i>Diabetes Mellitus (DM)</i>	18 (15%)
<i>Intersticiopathias (IPN)</i>	16 (13.3%)
<i>Renal polycystosis (ADPBB)</i>	12 (10%)
<i>Nondifferentiated nephropathy</i>	9 (7.5%)
<i>Uroobstructive nephropathy (UOP)</i>	7 (5.8%)
<i>Control group = 120</i>	Mean age = 58.5 ± 8.1

Patients with ESRD treated with repeated haemodialysis had a mean age of 59.5 ± 12.8 years. HD frequency was three times a week for a duration of 4 hours, while dialyses were carried out by use of a biocompatible halfsulphonic capillary membrane (F 6 HPS and F5 HPS, Fresenius&Hemomed) with a surface $\geq 1-1.3$ m², sterilized with high pressure steam. The control group of healthy examinees consisted of 120 persons (66 males and 54 females) with a mean age of 58.5 ± 8.1 years. The data were processed with a standard Windows statistical programme (Statistics for Windows software) version 6.0 A, Stat soft Inc. Tulsa, OK, USA).

Reference values of the examined parameters of lipid profile and apoproteins are presented in Table 2.

Table 2 – Табела 2

Referent values of investigated parameters
Референтни вредности на испитуваније параметри

Lipid profile	Reference values	Authors
TL	4–10g/l	Zollner & Kirsch [25]
TG	0.68–1.70 mmol/l	G. Buccola & H. David [26]
TCh	3.1–5.2 mmol/l	CC.Allain <i>et al</i> [24]
LDL-Ch	< 3.4mmol/l, increased risk: > 4.1 mmol/l	Friedewalde&Fredrickson[27]
HDL-Ch	> 1.6mmol/l, increased risk: < 0.9 mmol/l	G. Warnick <i>et al</i> [28]
ApoA-1 ApoB-100	ApoA-1 = 1.0–1.90g/l ApoB-100 = 0.5–1.60g/l	Umunoturbidim.-Rifai N [29]

The obtained lipid results (TCh, TG, HDL-ch, LDL-ch), ApoA-1 and ApoB-100 from patients with ESRD and those of the control group are presented in Table 3.

Table 3 – Табела 3

Results of laboratory investigations
Резултати од лабораторискије испитувања

	N ⁰	TCh mmol/l	TG mmol/l	HDL-ch mmol/l	LDL-ch mmol/l	ApoA-1 mg/l	ApoB-100 mg/l
<i>Patients on HD</i>	120	5.0 ± 1.25	2.64 ± 0.35	0.9 ± 0.35	3.46 ± 0.60	1.04 ± 0.38	2.78 ± 0.86
<i>Control group</i>	120	4.95 ± 1.22	1.30 ± 0.63	1.6 ± 0.71	2.75 ± 0.75	1.43 ± 0.43	1.05 ± 0.20
p		0.7541	0.0001	0.0001	0.0001	0.0001	0.0001

Table 3 shows a significant difference in the values of the greater part of parameters tested [*ApoA-1* (1.04 ± 0.38), *ApoB-100* (2.78 ± 0.86), *TG* (2.64 ± 0.35), *LDL-ch* (3.46 ± 0.60)] with $p < 0.0001$ except for TCh, in comparison with the results obtained from the control group [13, 14].

Discussion

Etiologic factors for dyslipidaemia are numerous in patients with ESRD treated by repeated HD. These factors include declined enzyme activity of lipoprotein lipase (LPL) and triglyceride hepatic lipase (HTGL), accumulation of uraemic toxins as well as high serum concentrations of ApoC-III and of parathyroid hormone (PTH) [6, 7, 8, 9, 50]. There are two large classes of circular lipoproteins that are distinguished on the basis of apolipoprotein composition (ApoA-1 and Apo-B) as basic constituents of apoproteins. The apolipoprotein which mainly contains ApoA-1 has a high density (HDL) and it is antiatherogenic, while Apo-B associates more lipids, it is a main constituent in the VLDL, IDL and LDL-ch structure and it is considered to be an atherogenic apoprotein. LDL lipoproteins, rich in a large content of Apo-B, are the most significant factor in the genesis of arterial atherosclerosis [35].

In conditions of uraemia, the reduced renal parenchyma cannot synthesize antiatherogenes (ApoA-1) or dissolve proatherogenic apolipoproteins (ApoB-100), which results in a TG increase of over 50% (increase of ApoB-100 and ApoC-III), and a decrease of HDL-ch by 20% [10, 11, 12]. During the last few years the interest in apolipoproteins (ApoA-1, ApoB-100...) as new risk factors for premature atherosclerosis in patients with ESRD has increased due to the kidney's involvement in the metabolism of apoproteins, particularly of apo(a) and of Lp(a) [4, 5].

Patients with ESRD had decreased values of TCh and HDL-ch and increased values of TG and LDL-h compared with the control group. Thus, it is supposed that low concentrations of TCh could be one of the factors for early premature atherosclerosis in patients with ESRD treated with repeated haemodialysis. There are data supporting the opinion that low plasma concentrations of HDL-ch are in close correlation with the decreased synthesis of Apo A-1 in patients with ESRD [20]. The protective effect of HDL-ch against early atherosclerosis is a result of its double role in the reverse transport mechanism of cholesterol. HDL-ch removes cell cholesterol and transfers the esterified cholesterol (from LCAT-Lecithin-cholesterol-acyl-transferase) to VLDL and LDL-ch helped by cholesterol ester transfer protein [21]. It was noticed that the transfer of cholesterol (Reverse Cholesterol Transfer, RCT) from HDL-ch to VLDL/LDL is less prevalent in the serum of HD patients in comparison with the control group that showed higher values of transport cholesterol [22]. Further studies

will confirm whether RCT progressively declines with the increase of kidney weakness. If RCT reflects the effectiveness of the reverse transport cholesterol mechanism, then low RCT indicates that HDL-ch can be less effective in uremic patients in the cholesterol transfer to remaining lipoproteins and that is why cholesterol demonstrates bigger tissue accumulation potential. This kind of defect can lead to accelerated atherosclerosis in ESRD. Statin therapy partially increased the level of serum HDL-Ch (10–15%), so it probably improves RCT in patients with ESRD treated with repeated haemodialysis. In patients undergoing haemodialysis, HTGL activity is significantly reduced in 33% while the activity of LCAT is reduced by 30% when compared with the control group [36]. The concentration of ApoA-1 in patients on HD is decreased as a result of the increased catabolism, and that of ApoA-2 due to decreased production [37]. Several studies have shown that the two groups of patients (chronic haemodialysis programme, CAPD) have significantly increased concentrations of ApoB-100 that contains ApoC-3 (ApoB: C-3) while the concentrations of TG, TCh, LDL-ch, ApoB-100 in patients treated with CAPD are higher in comparison with those in patients treated with the chronic haemodialysis programme. Patients with ESRD treated with repeated HD have markedly increased concentrations of TG, total Apo-E, ApoC, ApoB-100, ApoCnonB, Lp(a) and LDL-ch/HDL-ch, but they demonstrate a significant decline of ApoA-1, HDL-ch, HDL-ch/ApoA-1, ApoA-1/ApoB and ApoA-1/ApoC-3 in comparison with the control group of healthy examinees [38]. The comparative studies of lipo/apoprotein parameters in patients treated with different dialysis modalities (CAPD, HHDP) indicate that patients treated with CAPD are more affected by atherosclerosis, which is not confirmed by other authors [38, 39].

Additional studies are required with a greater number of patients with the aim of ascertaining precisely the manner and frequency of cholesterol transport as well as its connection with chronic renal insufficiency. The analysis of parameters of lipo/apoprotein status in our patients demonstrated that they had increased values of TG, ApoB-100 and decreased values of ApoA-1 and of HDL-ch in comparison with the control group. Many researchers such as Atmann, Oda, Mathur, Prichard and Milionis have confirmed disorder of apo/lipo-protein status of hHD and increased oxidized LDL-ch [40, 41, 42, 43, 44].

The decreased concentrations of Apo-A1 in patients with ESRD treated with repeated HD are closely linked with the decline of HDL-ch and with the increase of ApoB-100 concentrations that is followed by accumulation and increase of concentrations of VLDL and IDL [45, 46]. The initial stadium for the development of early atherosclerosis depends only on serum values of LDL-ch and ApoB-100 as well as declined values of ApoA-1. The atherogenic effect of dyslipidaemia in uraemic patients is indicated due to increased peroxidation of LDL-ch [47].

The use of biocompatible dialysis membranes ("High flux", *Polysulfon, PAN-AN69*), enables greater membrane absorption of atherogenic apolipoproteins and improvement of lipid profile as a result of decreasing concentrations of total ApoB-100 (for 30%) and AOPP (Advance Oxidized Protein Products) in uraemic patients [48, 49].

With regards to apolipoprotein abnormalities of ApoA-1 and ApoB-100 in our patients in relation to the basic kidney disease, the lowest values of ApoA-1 were found in patients with ADPBB (0.80 ± 0.26 g/l), UON (0.86 ± 0.24 g/l), GN (0.90 ± 0.30 g/l) and DM (0.94 ± 0.34 g/l). In patients with HTA, IPN and nondifferentiated nephropathy, the concentrations of ApoA-1 were over 1.0g/l ($P.B \pm 1.90$ g/l), which is in accordance with other studies, Kimak E [51].

As per the concentrations of ApoB-100, compared with the basic kidney disease, the greatest concentrations of this apoprotein were noticed in patients with GN, UON, D.M and ADPBB (from 2.98 ± 0.59 to 2.58 ± 0.61 g/l; $P.B = 0.5 \pm 1.60$ g/l), which is in accordance with the conclusion of Kandoussi AM [52].

Conclusion

In conclusion, we can point out that a knowledge of the etiopathogenic mechanisms of apo/lipoproteins and lipid abnormalities in patients with ESRD treated by repeated haemodialysis as well as revealing their role in early atherosclerosis may contribute to undertaking timely preventive measures (dietetic, healing, therapeutic) by which the incidence of dyslipidaemia will be reduced, the process of atherogenesis will be slowed down, and finally, the onset of cardiovascular and cerebrovascular disorders will be reduced. However, the fact is evident that additional long-term investigations with a greater number of patients are required, when the use of less traumatic methods (for instance Doppler measurements of lipid plaque of carotid arteries and other blood vessels) will confirm or deny their role as new, independent risk factors for the development of early atherosclerosis in patients with ESRD. Recognition of their physiologic functions – incomparable genetic polymorphism, broad inter-individual variations in plasma concentrations of ApoA-1 and ApoB-100 – can clearly contribute to preventing or postponing premature atherosclerosis, mainly presented as a coronary and/or cerebral disease in the uraemic population.

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Резиме

ЛИПИДЕН ПРОФИЛ И КОНЦЕНТРАЦИЈА НА ApoA-1 И ApoB-100 КАЈ ПАЦИЕНТИ СО ТЕРМИНАЛНА ХРОНИЧНА БУБРЕЖНА ИНСУФИЦИЕНЦИЈА ЛЕКУВАНИ СО ПОВТОРУВАНИ ХЕМОДИЈАЛИЗИ

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Нарушувањата на липидниот метаболизам кај болните со терминална хронична бубрежна болест се опишани во 1827 година од д-р Bright, посебно кај пациенти со нефротски синдром [1].

Познато е дека пациентите со терминална хронична бубрежна инсуфициенција (ТХБИ) презентираат клиничка слика на рана акцелерирана (прематурна) атеросклероза со сериозни кардиоваскуларни и церебрални компликации често присутни и во порана возраст споредено со општата популација. Денеска се смета дека уремиската дислипидемија перзистира со години напред пред започнување со хронично дијализно лекување и претставува основен ризик фактор за рано започнување на процесите на атерогенеза. Затоа анализирањето на аполипипротейнските и липидните абнормалности како и нивниот етиопатогенетски механизам кај болните со ТХБИ, лекувани со повторувани хемодијализи во фазата на иницирање на дијализата (први 6 месеци), може видно да придонесе за преземање на правовремени превентивни мерки (диететски, лечебни) со што ќе се намали честотата на аполипипротейнските и липидните абнормалности, а со тоа и проце-

сите на раната атеросклероза со сите нејзини компликации кај пациентите со ТХБИ [2].

Нарушувањата на аполипопротеинскиот метаболизам се сметаат за еден од најважните фактори за рана атеросклероза кај пациентите со ТХБИ [3].

Клучни зборови: аполипопротеин А-1(АроА-1), аполипопротеин В-100 (АроВ-100), терминална хронична бубрежна инсуфициенција (ТХБИ), липиден профил (тотален холестерол-ТCh, триглицериди-TG, HDL-холестерол, LDL-холестерол), хемодијализа, рана атеросклероза.

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