Original scientific paper
616.915-085.272.4:616.61-008.64-78-052

EFFECTS OF STATINS IN THE TREATEMENT OF UREMIC DYSLIPIDEMIA

Muhamedin Rushiti[1,2], Teuta Emini[2], Blerim Rustemi[2]

[1]University of Tetova, Faculty of Medical Sciences
[2]Clinic Hospital – Tetovo
Correspondin author: muhamedin.rushiti@unite.edu.mk

Abstract

Cardiovascular disease further remains as the main cause of mortality in patients with kidney diseases . Uremic dysfunction and apolipoprotein metabolism disorders are counted as a wellknown risk factor of cardiovascular disease (CVD) in patients with chronic kidney disease. A large number of studies have reported significant results of studies on the effects of hypolipemic drugs in the treatment of uremic dyslipidemia, a group of scientists reported positive effects while the other group is the opposite, the role of hypolipemic therapy in HD treated uremic patients is controversial and still remains confusing, wider and larger patient studies are needed to document the positive effects of statins on the treatment of uremic dyslipidemia. Numerous epidemiological studies have verified a high correlation between high LDL-ch and TG serum levels and lower proloquent HDL-ch cholesterol and high risk incidence of cardiovascular disease in predial and uremic patients treated with HD. Otherwise the role of dyslipidemia in the pathophysiology of atherosclerotic diseases in patients with damage kidney function remains still controversial. Some studies have shown a positive relations between cholesterol values and risk of disease in patients with ESRD, while others failed to find any significant correlation. Finally, several studies suggested a reverse relations between serum cholesterol values and mortality in patients with ESRD patients. Low-Density Cholesterol (LDL-ch), High-Density Cholesterol (HDL-ch) and plasma Triglyceride concentration were determined in patients with ESRD treated by chronically repeated hemodialysis=N°-80 befrore and treatment of 3 months with 20 mg *statins* (once daily, after dinner). In addition, the plasma activity of enzymes (Aspartat Aminotransferasae-AST,Alanin Aminotransferasae-ALT, CPK, CK-MB, Alkaline Phosphatasae (AP), Lactat Dehidrogenasae (LDH), possibly involved as a markers of hepatic or muscle toxicity were detected as well. Results shows that the Low Densitty Choleste-rol (LDL-ch) and TG concentrations were significantly higher in patients with ESRD submitted to chronic Haemodialysis (HD) than in control subjects matched by gender and age: $p< 0.005$. The High-Density Cholesterol (HDL-ch) concentration, before treatment with statins in investigated patients, was a near the normal value-1.20±0.30 mmol/l for men and 1.30±0.50 mmol/l for women, referent values in a controls: 1.65±0.60 mmol/l. The terapy with statins was effective concerning the LDL-ch and TG and theirs concentration were significantly diminished: $p <0.005$-0.0001. The HDL-ch concentration after statins treatment was a just higher than the pretreatment values (1.40 ±0.60 for men and and- 1.35±0.40 mmol/l for women) but without statistical significance :$p < 0.26$-0.75. The activity of tested hepatic and muscle enzymes (AP, AST, ALT, CPK, CK-MB) before and treatment with statins in same group of dialyzed patients was statistically lower after therapy: 159.40 ±25.20 vs130.50 ±37.40 U/l, $p<0.02$ for men , and 162.10 ±32.60vs135.40 ±36.40 U/l, $p<0.005$ for women. Having in mind the newly accepted theories for accelerated atherosclerosis in patients with ESRD treated with HD, the medical control of lipid profile rise considerably important.

Keywords: statins, Low- Density Cholesterol (LDL-ch), High-Density Cholesterol (HDL-ch), Triglycerides (TG), Haemodialysis (HD), ESRD (End-Stage-Renal-Disease).

INTRODUCTION

Purpose of the present study was to evaluate lipids abnormalities in patients with End-Stage-Renal-Disease treated with long term haemodilaysis more than 6 years and the effect of statins (20 mg once daily after evening). In addition we compared lipid and enzymes levels between the same groups of Chronic renal failure (CRF) patients (male and females on maintenance HD) before and after treatment with statins. Special emphasis was placed on evaluating

abnormalities in HDL-ch metabolism that are currently believed to control the progress of aterogenesis and cardiovascular and cerebrovascular diseases.

Materials and methods

The study included 80 patients (No-80, 45 males and 35 females) treated on maintenance haemodialysis 6 or more years. The ages of the patients ranged from 19-70 years, with a mean of 58.0 ±13.5 years for men and 59.0 ± 14.0 years for women. Control subject were 80 healthy people (45 men and 35 women) in the age range of 19 to 67 years (mean:55.0 ± 9.80). Lipid Measurement: Triglycerides TG), serum total cholesterol (TCh) and high-density cholesterol (HDL-ch) were determined following the methods describing by Allain, Boccola and David. The serum activity of hepatic enzymes was determined following the routinely accepted methods in clinical chemistry.

RESULTS

Serum lipid in control subjects (C), maintenance dialyzed uremic patients before Atorvox therapy (HD) and maintenance dialyzed uremic pts two months after treatment with Atorvox (AHD-) are compared and presendet in table 1. Serum lipids in controlled subjects (C), maintenance dialyzed uremic patients before Atorvoxtherapy (HD) and dialyzed uremic pts maintenance two months after treatment with Atorvox (AHD-) were compared and found in Table 1.

Table 1. Lipid and Lipoprotein plasma of study subjects

		Control subjects(C)	**HD pts before Atorvox**	**AHD pts**
TCh	Males	4.90± 1.20	**5.80±1.30**	**5.60.±1.20**
	Females	4.90± 1.20	**5.75±1.15**	**5.70± 1.08**
TG	Males	1.34± 0.40	**3.20±1.59[1]**	**2.50 ±0.50[5,7]**
	Females	1.34± 0.40	**3.15 ±0.87[2]**	**2.60±0.70[6,9]**
HDL-Ch	Males	1.40±0.60	**1.25±0.50**	**1.34±0.50**
	Females	1.40± 060	**1.46±0.40**	**1.32±0.46**
LDL-Ch	Males	2.95± 1.02	**3.90±1.08[3]**	**2.48.±0.46[9]**
	Females	2.95± 1.02	**3.97±0.95[4]**	**2.50±0.50[10]**
LDL/HDL-Ratio	Males	1.70±1.42	**3.20±2.16**	**1.80±0.90**
	Females	1.70± 1.42	**3.16±1.86**	**1.88±1.10**

Data are given with mean ±SD

[1]-p<.001 compared to controls; **[2]-p<.001** compared to controls; **[3]- p<.05** compared to controls; **[4]- p< .05** compared to controls;**[5]-p < .01**compared to controls pre-treatment value**;[6]-p<. 01**compared to controls; **[7]- p<.05**compared to pre-treatment value ; **[8]- p< .01**compared to

pre-treatment value**; [9] – p< .001** compared to pre-treatment value ; **[10]-p< .001** compared to pre-treatment value

In the present study the lipid serum levels in control subjects are significantly different (lower values) for TG and LDL- ch in comparison with investigated HD- patients group (males and females non treated with Atorvox). Only the TG–concentration in AHD- patients group (males and females treated with Atorvox) demonstrated significantly higher value in comparison to controls. In the same patients groups (males and females non –treated or treated with Atorvox) the significant diference in serum levels is noted for triglycerides and LDL-cholesterol(evidently lower values after therapy with $p_{7\text{-}10}p< 0.05$ to 0.001 respectively). The serum HDL-ch concentration demonstrates a clear elevation trend for AHD patients, but without statistical significance. The LDL\HDL-Ratio in ESRD patients on maintenance haemodialysis before treatment with Atorvox was higher (about 3) in comparison with the controls (1.70). After Atorvox therapy, the LDL\HDL- ratio was near the normal value encountered in controls (1.80 for males and 1.88 for females). Thus***, the LDL\ HDL- ratio may be a useful marker for successful hypolipemic treatment.*** Patients with reduced renal function (and especially treated with maintenance dialysis) during the treatment with statins and\or with fibrates may develop easier myolysis (rhabdomyolyisis) or hepatic lesions. Consequently, we have tested the plasma activity for many enzymes (alkalinephosphatasae /AP/, ALT,AST CPK, CK- mb and LDH) before starting the hypolipemic therapy and after the two (2) months treatment with Atorvox (20 mg, once a day, in the evening, after dinner). The table 2, demonstrates the values for tested enzymes before and after treatment with Atorvox.

Table 2. Muscle and hepatic enzymes activity before and after treatment with Atorvox of study subjects

Enzymes activity (U/L)	**Gender**	**Before the therapy**	**After the therapy**
Alkaline phosphatasae (AP)	Males	127.20 ± 60.50	110.30 ±32.80*
	Females	130.00± 98.00	118.60 ± 75.00*
Aspartate amino-transferasae (AST)	Males	34.80 ± 24.00	38.00 ±23.00*
	Females	36.50 ± 28.60	36.30 ±24.00*
Alanine amino-transferasae (ALT)	Males	34.00±15.90	31.24±17.90*
		38.60 ± 19.80	35.00 ± 18.70*
Creatininekinasae (CK)	Males	158.50 ±32.00	101.60 ±30.40[1]
	Females	138.00 ±24.10	96.70 ±31.60[2]
Creatininekinasae-mb (CK-mb)	Males	6.00 ± 4.20	2.80 ±1.70[3]
	Females	5.30 ±4.30	3.50 ±2.00*
Lactate dehydrogenasae (LDH)	Males	159.40 ±25.20	130.50 ±37.40[4]
	Females	162.10 ±32.60	135.40 ±36.40[5]

Difference non-significant:**[1]- p<.01; [2]- p<.02; [3]-p <001; [4]- p< 02; [5]-p <05**

We have not demonstrated increase in activity for hepatic or muscle enzymes after two months Atorvox therapy. Paradoxically, we have noted a significantly decreased serum enzyme activity for CK(males and females), CK-mb (males) and LDH (two sexes). For this results we have not a valid explanation. Possibly the results are due to the small group of investigated patients. Only one patient demonstrated a nausea without vomiting in the first few days after beginning

the therapy with Atorvox, consequently the treatment was continued successfully other problems.

RESULTS

Serum lipid in control subjects (C), maintenance dialyzed uremic patients before statins therapy (HD) and maintenance dialyzed uremic pts two months after treatment with statins (SHD-) are compared and presented in table 1. In the present study the lipid serum levels in control subjects are significantly different (lower values) for TG and LDL-ch in comparison with investigated HD- patients group (males and females non treated with statins. Only the TG–concentration in statins hemodialysis patients group (males and females treated with statins) demonstrated significantly higher value in comparison to controls. In the same patients groups (males and females non-treated or treated with statins) the significant diference in serum levels is noted for triglycerides and LDL-cholesterol (evidently lower values after therapy with $p_{7\text{-}10}p < 0.05$ to 0.001 respectively).The serum HDL- ch concentration demonstrates a clear elevation trend for statins hemodialysis patients, but without statistical significance. The LDL\HDL-Ratio in ESRD patients on maintenance haemodialysis before treatment with statins was higher (about 3) in comparison with the controls (1.70). After statins therapy, the LDL\HDL- ratio was near the normal value encountered in controls (1.80 for males and 1.88 for females). Thus, the LDL\ HDL-ratio may be a useful marker for successful hypolipemic treatment. Patients with reduced renal function (and especially treated with maintenance dialysis) during the treatment with statins and\or with fibrates may develop easier myolysis (rhabdomyolyisis) or hepatic lesions. Consequently, we have tested the plasma activity for many enzymes (alkalinephosphatasae /AP/, ALT,AST CPK, CK- mb and LDH) before starting the hypolipemic therapy and after the two (2) months treatment with statins (20 mg, once daily, in the evening after dinner). The table 2, demonstrates the values for tested enzymes before and after treatment with statins. We have not demonstrated increase in activity for hepatic or muscle enzymes after two months statins therapy. Paradoxically, we have noted a significantly decreased serum enzyme activity for CK (males and females), CK-mb (males) and LDH (two sexes). For this results we have not a valid explanation. Possibly the results are due to the small group of investigated patients. Only one patient demonstrated a nausea without vomiting in the first few days after beginning the therapy with statins, consequently the treatment was continued successfully other problems. The effect of statins on the uremic dyslipidemija is investigated in the several studies especially in the patients treated by maintenance haemodialysis or continuous ambulatory peritoneal dialysis. The dose of 5mg\day statins for 24 weeks appears to be safe and effective in HD-patients with hypercholesterolemia (signifycantly diminished total cholesterol and LDL-Ch (20). Saltissi D et al. describe the safety and efficacy of statin in CAPD or maintenance HD patients (simvastatin 5-20 mg\24h, for 24 weeks). In maintenance dialyzed patients they found LDL-Ch levels reduction for 33% . In our study four times higher dose of statins (20 mg\day)for 3 months is also safe with the following results : significantly decreased levels for tryglicerides (by 20.9% for men and 18.5%for women) and LDL-Ch(by 31.5% for men and 35.8% for women respectively). Moreover, statins may exhibit additional inhibitory effect on the atherogenesis, such as a modulation of the immune system as triggered by oxidatively modified LDL during dialysis process (as an example of chronically repeated oxidative stress) and a reduction of the inflammatory markers {(presumably–reactive protein.

CONCLUSION: Uremic dyslipidemi is a very common complication in patients with End Stage renal disease (ESRD) and appears in the early stages of the disease. Contemporary studies show that uremic dyslidemia significantly affects the occurrence of cardiovascular disease and the deterioration of renal function. Therefore, we consider and propose that the use

of hypolipemic therapy (statin, fibrates, niacin, cholestipol, cholestyramine, omega 3, etc.) should be a major obligation of nephrologists and doctors in order to prevent the consequences of hyperlipidemia in the appearance of early atherosclerotic processes to the cardiovascular, cerebrovascular and peripheral system in the treatment of this common occurrence in patients with chronic renal failure.

DISCUSSION

Although it has been suggested that uremic patients on maintenance haemodialysis develop atherosclerosis at an accelerated rate and have a high mortality due to atherosclerosis complications, definitive studies linking uremic lipid abnormalities and rates of growth of angiographycally or ultrasonographycally demonstrated atheroma are not available. Furthermore, it has been argued that the high mortality is contributed by patients with prior coronary artery disease. There have been several reports documenting lipid and lipoprotein abnormalities in uremic patients on maintenance haemodialysis. These patients usually have slightly reduced levels of serum cholesterol, high plasma tryglicerides, low- to- normal LDL cholesterol levels and a marked decrease in HDL cholesterol when compared with normal controls. The low HDL cholesterol may be involved in the development of accelerated atherosclerosis in these subjects. Undialyzed patients with ESRD had serum total cholesterol levels similar to the controls, HDL-ch concentration lower than the controls, but higher than those in the haemodialysis patients . The patients with pre-dialysis chronic renal failure (CFR) suffering from diastolic hypertension, proteinuria (> 3 g/24 h) and higher LDL-ch level ($p=0.04$) present a higher decline of residual renal function and spider progression of renal disease in pre-dialysis stage . There are data supporting the view that low plasma HDL-ch levels in patients with CRF are related to decerease in the synthetic rate of Apolipoprotein A-I/HDL-ch. The putative protective effect provided by HDL-ch against atherosclerosis is attributed to its two-step role in the reverse cholesterol transport mechanism. In this respect HDL-ch removes cellular cholesterol at the tissue level and, secondly, transfers esterified cholesterol (by LCAT) to VLDL and LDL-ch by the action of the cholesteryl ester transfer protein (FuhMMt *et al.,* 1990). It was found that the rate of cholesterol transfer (RCT) from HDL-ch to VLDL/LDL was lowest in the serum haemodialyzed patients. The controls had a highest value for RCT followed by that in undialyzeduremics (Dieplinger *et al.,* 1986). Whether RCT progressively decreases with increasing renal failure will require study. If RCT reflects the efficiency of the reverse cholesterol transport pathway, then a low RCT indicates that HDL-ch in uremics might be effective in the transfer of cholesterol to others lipoproteins and , thus, indicates a greater potential for tissue cholesterol accumulation. Such a defect could lead to accelerated atherosclerosis in ESRD patients. The treatment with Atorvox (in our cases) trend to increase the serum HDL-ch levels and probably to improve the RCT. Several studies found low LCAT activity in HD patients (Krolevski *et al.,* 1994, Tsimihodimos *et al.,* 2008), but in contrast, Bories et al. (Boeries *et al.*, 1982) found normal LCAT activity in the patients. The same authors found it in undilayzed uremic patients to be lower than both the controls and the haemodialyzed patients, by using the proteoliposome method following Chen and Allbers (Gupta *et al.,* 1992). Finally the abnormalities in LCAT, RCT and HDL-ch level coud predispose these patients to the development of accelerated atherosclerosis. Hyperlipidemia (especially native, glucated and oxidized LDL-ch) may play a role in the progression of diabetic chronic renal disease undergoing non-enzymatic glutation or oxidation in vivo . Consequently, its binding and uptake by the LDL-receptors of mesangial cells decreases and may slow its catabolism. Furthermore, LDL components contributing to glomerular pathology (Krolewski *et al.,* 1994). Among the many baseline variables examined (like proteinuria in patients with diabetic nephropathy), only elevated total (and LDL) cholesterol and systemic arterial

hypertension were predictors of a rapid loss of renal function and highest risk of death due to cardiovascular causes in the case of CRF (Nishikawa *et al.,* 1997). The effect of statins on the uremic dyslipidemija is investigated in the several studies especially in the patients treated by maintenance haemodialysis or continuous ambulatory peritoneal dialysis. The dose of 5mg\day Atorvox for24 weeks appears to be safe and effective in HD-patients with hypercholesterolemia (significantly diminished total cholesterol and LDL-Ch (Saltissi *et al.,* 2002). Saltissi Detal describe the safety and efficacy of statin in patients undergoing CAPD or maintenance haemododialysis (simvastatin 5-20 mg\24h, for 24 weeks). In maintenance dialyzed patients they found LDL-Ch levels reduction for 33% (18,19). In our study four times higher dose of Atorvox (20 mg\day)for 3 months is also safe with the following results : significantly decreased levels for triglycerides (by 20.9% for men and 18.5%for women) and LDL-Ch(by 31.5% for men and 35.8% for women respectively). Moreover, statins may exhibit additional inhibitory effect on the atherogenesis, such as a modulation of the immune system as triggered by oxidatively modified LDL during dialysis process(as an example of chronically repeated oxidative stress) and a reduction of the inflammatory markers (presumably–reactive protein (Van *et al.,* 2003).

REFERENCES

[1]. FuhMMT, LeeCM, Jeng CY, Shen DC, Shien SM, Reaven GM, Chen YDI. Effect of chronic renal failure on high-density lipoprotein kinetics. Kindney Int 1990;37:1295-1300

[2]. Fielding CJ, Fielding PE. Cholesterol transport between cells and body fluids. Med Clin North Am 1982;66:363-366

[3]. Dieplinger H, Schoenfeld PY, Fielding CJ. Plasma cholesterol metabolism in end stage renal disease: differences between treatment by haemodialysis and peritoneal dialysis. J Clin Invest 1986;77:1071-1083.

[4]. Lutfi Zulbeari. Profilna Dislipidemija i Apolipoproteinskite Aberacii kaj Pacienti Lekuvani so Povtoruvani Hemodijalizi. 2009, Doktorska Disertacija; Univerzitet “Sv. Kiril i Metodij, Medicinski Fakultet-Skopje.

[5]. Bories PC, Subbaiah PV, Bagdade JD. Lecithin: cholesterolacyltransferase activity in dialyzed and undialyzed uremic patients. Nephron 1982;25:22-27

[6]. Chen CH, Albers JJ. Characterization of proteoliposomes containing apoproteinA-I; a new substrate for the measurement of lecithin: cholesterolacyltransferase activity. J Lipid Res 1982;23:680-691

[7]. Gupta S, Rifici V, Crowley S, Brownlee M, Shan Z, Schlondorff D. Interactions of LDL and modified LDL with mesangial cells and matrix. Kidney Int 1992;41:1161-1169

[8]. Krolewski AS, Warram JH, Christlieb AR. Hypercholesterolemia-a determinant of renal function loss and deaths in IDDM patients with nephropathy. Kidney Int 1994;45 (suppl145): pp S125-S131

[9]. Nishikawa O et al. Effect of simvastatin on the lipid profile of haemodialysis patients. Kidney Int 1999:71(Supp2):pp S219-S221

[10]. Saltissi D, Morgan C, Rigby RJ, Westhuyzen J. Safety and efficacy of simvastatin in hypercholesterolemic patients undergoing renal dialysis. Am J Kidney Dis 2002:39(2):283-290

[11]. Van den Akker JM, Bredie SJ, Diepenveen SH,van Tits LJ, Stalenhoef AF, van Leusen R. Atorvastatin and simvastatin on haemodialysis; effects on lipoproteins, C-reactive protein and in vivo oxidized LDL. J Nephrol 2003;16(2):238-244