ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN – POLONIA
VOL. LIX, N 1, 86 SECTIO D 2004

Chair and Department of General Surgery and Transplantology
Department of Nephrology, Department of Clinical Analytics
Skubiszewski Medical University of Lublin
District Specialist Hospital of Stefan Cardinal Wyszyński in Lublin

KRZYSZTOF JANICKI, JANUSZ SOLSKI, LUCYNA JANICKA,
ELŻBIETA KIMAK, ANNA BEDNAREK-SKUBLEWSKA,
SEWERYN STETTNER, GRZEGORZ MOLAS

Lipid and apolipoproteins (ApoAI, ApoB, Apo CIII, ApoE) disturbance in hemodialysis (HD) and renal transplant (Tx) patients

The lipoprotein metabolism is altered in patients with chronic renal insufficiency as well as in patients on maintenance hemodialysis (1, 12). Lipoprotein abnormalities are often present in renal transplant patients (3). Atherosclerotic cardiovascular disease is one of the major causes of death after Renal Replacement Therapy. Atherosclerotis associated with dyslipidemia is a major cause of morbidity and mortality after renal transplantation (4, 8). Hypertriglyceridemia has also been reported to be a risk factor of graft loss due to chronic rejection (10).

The aim of our study was estimation of lipid and apolipoprotein parameters in patients after transplantation of kidneys (Tx) in comparison with chronic dialysed patients (HD). Simultaneously, we wanted to receive the answer to the question whether there exists a correlation between the ascertained lipoprotein disturbances and period of time which passed from executed transplantation of kidneys.

MATERIAL AND METHODS

The study was carried out on 40 stable patients on HD (20 female and 20 male) with an average age of 49.9 years (range 24 to 76 years). The mean duration of HD 47.7 months (rage 5 to 192 months). The underlying cause of chronic renal failure included chronic glomerulonephritis in seven patients, chronic interstitial nephritis in six patients, obstructive nephropathy in seven patients, nephrosclerosis in six patients, polycystic kidney disease in six patients, reflux nephropathy in three, patients bilateral nephrectomy in two patients, and miscellaneous in three patients. Hemodialysis was performed 3.5–4.5 hours per session, three times per week, all using polysulfone hollow fibre dialyzers with bicarbonate containing dialysate. 30 hemodialysis patients were on erythropoietin treatment and 15 patients were receiving antihypertensive agents. Investigations refer also to a group of 15 patients after transplantation. The control subjects were 40 healthy individuals matched for average age 52.3–7.6 and gender (20 female and 20 male) who had not known disease and who were not taking any medications. Blood samples were taken from both patients and controls after a 14-hour overnight fast for the determination of lipid and apolipoproteins parameters. Following parameters were estimated in

plasma: total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), apolipoprotein ApoAI, ApoB, ApoCIII, and ApoE. The TC/HDL-C ratio, HDL-C/ApoAI ratio, ApoE:B ratio, ApoCIII non B ratio, ApoB:ApoCIII ratio, Apo AI/ApoCIII ratio, ApoB/ApoCIII ratio were also evaluated. Routine laboratory parameters such as the level of urea, creatinine, uric acid and albumin were determined by using Roche Cobas Integra Analyzer, and electrolyte concentration with ionoselective electrodes Kone analyzer. Lipid and apolipoproteins were also determined on Cobas Integra Analyzer.

Total cholesterol was determined using the enzymatic-colorimetric method (cholesterol CHOD-PAP), HDL-cholesterol (HDL-C) was measured after precipitation with phosphotungstic acid and magnesium ions, LDL-cholesterol. (LDL-C) was calculated according to the Friedwald formula.

Triglycerides (TG) were determined using standard enzymatic techniques (Roche Kit). ApoAI, ApoB were measured by Roche Kit using the immunoturbidimetric methods. The total ApoCIII (ApoCIII), ApoCIII present in the particles without ApoB (ApoCIII non B), total ApoE (ApoE), ApoE present in the particles without ApoB (ApoE non B) were measured by electroimmunodiffusion using commercial Kits (Sebia Issy, Moulineaux, France), but particles containing ApoB and ApoCIII (ApoB:CIII) were calculated from the difference between ApoCIII and ApoCIII non B, and particles containing ApoB and ApoE (ApoB:E) were calculated from the difference between ApoE and ApoE non B. The obtained results were statistically analysed. Statistical analysis was performed using ANOVA method from STATISTICA – statistical software on PC computers. Correlation between variables was evaluated using the linear regression method.

RESULTS

Clinical and biochemical parameters in renal transplant patients (Tx) are presented in Tables 1 and 2. The concentrations of lipids and apolipoproteins and also lipoprotein ratios in the control group as well as in the HD patients and Tx patients are summarised in Table 3. Laboratory parameters in hemodialysed patients are presented in Table 4. There was some evidence that the levels of TG and ApoCIII, and of ApoE and TC/HDL-C and of ApoCIII non B, and of ApoCIII:B were significantly increased, moreover the levels of HDL-C, and of ApoAI and HDL-C/ApoAI and of ApoAI/ApoCIII and ApoB/ApoCIII were decreased in HD patients compared to the control group. There were increased levels of TG, ApoCIII and ApoCIII non B and of ApoB/ApoCIII ratios, and decreased levels of ApoAI/ApoCIII in renal transplant patients as compared to the control subjects. Otherwise, there were significantly higher levels of HDL-C and ApoAI and of HDL-C/ApoAI and ApoCIII non B, and lower levels of ApoE, ApoE/ApoB and ApoCIII:B at renal transplant patients as compared to these of HD patients.

There was a significant inverse correlation of the time which passed from executed renal transplantation and CIII:B ratio ($r = -0.67$; $p < 0.01$) in renal transplant patients (Fig. 1).

Table 1. Clinical characteristics of renal transplant recipients (CGN – chronic glomerulonephritis; IN – interstitial nephritis)

Patient initials	Sex	Age (years)	Weight (kg)	Underlying disease	Blood pressure (mmHg)	Time on HD (months)	Time since transplantation
Z.J	M	48	65	CGN	150/80	11	12
D.A.	M	42	72	CGN	140/90	29	17
W.D.	F	43	51	CGN	130/85	36	41
G.R.	M	43	51	CGN	140/80	57	38
T. C.	M	60	70	CGN	150/90	39	40
Pa. A.	M	38	70	CGN	150/100	29	29
B. A.	M	34	71	CGN	160/90	26	48
P. A.	M	31	61	CGN	150/95	27	23
P. Ad.	M	30	72	CGN	140/80	22	22
N. I.	F	47	65	IN	140/80	28	12
W. A.	M	24	67	CGN	130/75	25	33
C. T.	F	45	89	CGN	120/80	75	33
C. I.	M	35	76	CGN	170/100	42	3
P. M.	M	25	64	CGN	130/80	45	10
P. S.	M	53	70	CGN	130/80	96	3
Mean ± SD		39.9 ± 10.2	68.3 ± 8.3			39.1 ± 22.1	24.3 ± 14.4

Table 2. Biochemical parameters in patients after transplantation (RBC – red blood cell count, WBC – white blood cell count, PLT – platelet count)

Patients initials	Urea (mg/dL)	Creatinine (mg/dL)	Uric acid (mg/dL)	Albumin (g/dL)	Proteinuria (yes/no)	Haemoglobin (g/dL)	Haematocrit (%)	RBC (x 10^9/L)	WBC (x 10^6/L)	PLT (x 10^9/L)	Mg (mEq/L)
Z. J.	37.0	1.00	6.6	4.1	no	14.5	42.5	4460	7600	260	1.6
D. A.	65.0	1.50	5.5	4.2	no	12.0	36.0	4450	6700	265	1.5
W. D.	40.0	1.00	5.3	4.3	no	16.0	45.0	5250	7000	181	1.3
G. R.	68.0	2.10	8.6	3.9	no	11.3	33.0	3350	5400	186	1.7
T. C.	70.0	1.30	8.6	4.0	no	12.6	36.0	3490	9600	288	1.5
Pa. A.	64.0	1.50	5.5	3.9	no	15.0	45.0	4700	7800	180	1.3
B. A.	120.0	3.10	7.0	3.5	yes (1.5 g/24h)	11.3	35.0	3540	6400	181	1.3
P. A.	60.0	2.00	6.8	4.1	no	14.3	42.0	4700	7500	116	1.5
P. Ad.	30.0	1.40	5.9	4.0	no	14.4	42.0	4400	8000	192	1.5
N. I.	50.0	1.25	6.4	4.2	no	13.9	39.0	4200	6500	165	1.5
W. A.	125.0	3.00	7.8	3.8	yes (2.5 g/24h)	12.3	34.0	3800	9000	181	1.3
C. D.	72.0	1.60	11.0	4.2	no	13.3	38.0	3730	6600	243	1.5
C. I.	56.0	1.80	5.7	3.9	no	14.0	41.0	4100	9600	220	2.1
P. M.	90.0	3.00	6.1	3.8	yes (0.4 g/24h)	11.0	36.0	3500	6800	210	1.5
P. S.	100.2	2.10	6.1	3.9	yes (1.0 g/24h)	9.9	35.0	3600	6700	260	1.5
Mean ± SD	69.8 ± 28.3	1.8 ± 0.7	6.9 ± 1.6	4.0 ± 0.2		13.1 ± 1.7	38.6 ± 4.0	4085 ± 565	7413 ± 1218	209 ± 47	1.5 ± 0.2

Table 3. Serum lipoprotein parameters in HD, Tx patients and controls (mean ± SD)
$p < 0.05$; a – HD versus control; b – Tx versus control; c – Tx versus HD; NS – not significant

Parameter	HD (n = 40)	Tx (n = 15)	Controls (n = 40)
TG (mg/dL)	122.68 ± 39.95 a	126.00 ± 56.36 b	82.70 ± 16.32
TC (mg/dL)	183.07 ± 56.59	208.42 ± 45.48	180.90 ± 60.03
HDL-C (mg/dL)	40.98 ± 11.87 a	58.50 ± 18.48 c	60.30 ± 12.68
Apo AI (mg/dL)	131.18 ± 20.68 a	153.21 ± 36.80 c	157.60 ± 16.72
Apo B (mg/dL)	92.58 ± 30.13	88.14 ± 24.94	90.20 ± 14.76
Apo CIII (mg/dL)	3.973 ± 1.238 a	4.153 ± 0.992 b	2.640 ± 0.519
Apo E (mg/dL)	8.366 ± 3.133 a	6.547 ± 2.081 c	6.180 ± 0.919
TC/HDL-C	5.04 ± 1.91 a	3.91 ± 1.56	3.41 ± 0.73
HDL-C / Apo AI	0.30 ± 0.06 a	0.38 ± 0.09 c	0.38 ± 0.049
Apo B : ApoE (mg/dL)	3.703 ± 1.865 a	1.670 ± 0.693 c	1.970 ± 0.778
Apo CIII non B (mg/dL)	2.603 ± 0.902 a	3.487 ± 0.953 b, c	0.860 ± 0.406
Apo B : CIII (mg/dL)	1.398 ± 0.738 a	0.693 ± 0.252 c	0.780 ± 0.225
Apo AI / Apo CIII	35.9 ± 9.9 a	36.0 ± 9.7 b	61.0 ± 9.3
Apo B / Apo CII	24.8 ± 9.1 a	91.4 ± 21.6 b, c	34.8 ± 7.2

Table 4. Laboratory parameters in hemodialysed patients (mean ±SD)

		X	SD
Urea (mg/dL)	before HD	146.74	27.86
	after HD	56.08	18.26
Creatinine (mg/dL)	before HD	10.07	2.87
	after HD	4.63	1.70
Uric acid (mg/dL)	before HD	5.56	1.30
	after HD	1.58	0.89
Magnesium (mEq/L)		2.089	0.278
Ferritine (ng/mL)		234.27	212.70
Iron (µg/dL)		54.75	16.06
RBC (x 10^9 / L)	before HD	2.99	0.42
	after HD	3.29	0.53
Haemoglobin (g/dL)	before HD	9.58	1.33
	after HD	12.82	1.44
Haematocrit (%)	before HD	28.4	3.96
	after HD	30.77	5.07
WBC (x 10^6/L)	before HD	6.43	1.40
	after HD	6.22	1.81
Fibrinogen (mg/dL)		334.3	67.67
Albumin (g/dL)		4.01	0.47

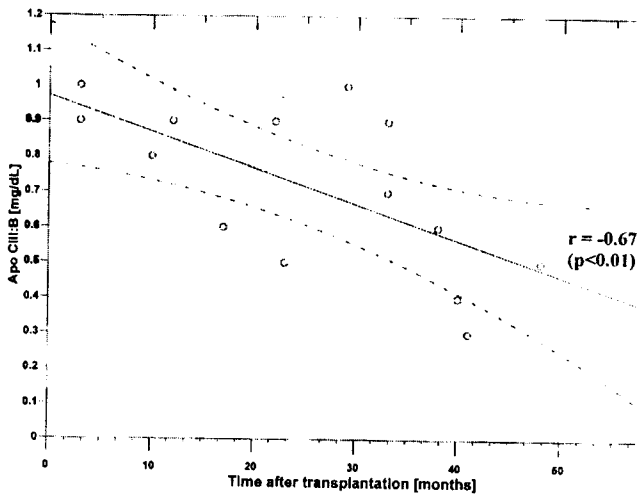

Fig. 1. Correlation between serum Apo CIII:B concentration and after transplantation

DISCUSSION

In our study both groups of HD and Tx patients have abnormal serum lipids and lipoproteins profiles. Hemodialysis patients exhibit more atherogenic lipoprotein profile than Tx patients. Hyperlipidemia in patients with renal insufficiency is due both to increase of production and to the reduction of degradation of lipoproteins and also, a result of a complex of metabolic changes associated with decreased renal function (15). The causes of dislipidemia in hemodialysis patients are multifactorial. The main metabolic abnormality of the lipoprotein profile is delayed catabolism of triglyceride-rich ApoB containing lipoproteins (12). The process is caused by decreased activity of lipolytic enzymes in triglyceride metabolism (such as lipoprotein lipase LPL, and hepatic triglycerides lipase – the two principal enzymes in triglyceride metabolism). Data showed in the literature suggest the prevalence of hyperlipidemia after renal transplantation ranges from 16% to 72% (9, 11). Several factors contribute to post-transplant hyperlipidemia, including impaired graft function, dietary habits and use of immunosuppressive and antihypertensive medications. Cyclosporin A, especially at higher doses, employed in renal transplant recipients may significantly reduce the metabolic degradation of LDL particles (2, 7, 14).

In our study, the group of Tx patients was too small to investigate the effect of differences at immunosuppressive therapy. Our HD and Tx patients had increased serum triglycerides and HD patients decreased HDL-C levels compared to control subjects. Low levels of HDL cholesterol are most likely due to hypertriglycidemia. Low HDL cholesterol levels in uremic patients could also be attributed to other mechanisms, such as decreased hepatic lipase activity and LCAT, and decreased ApoAI synthesis (13). ApoAI levels were decreased in our hemodialysis patients compared to the controls, the ratio of HDL/ApoAI was also significantly lower. These findings implicate the existence of qualitative changes in the composition of the HDL-C (5). In our experiment we did not observe notable differences between total and LDL cholesterol levels, between HD patients and Tx patients and the control group. We noticed that HD and Tx patients had increased level of ApoCIII. Furthermore, HD patients had increased level of ApoE. It is well known that ApoCIII is a potent inhibitor of LPL activity. We found a significant inverse correlation between the time which passed from executed renal transplantation and CIII:B ratio, which means the diminished risk of development of arteriosclerosis (Fig. 1). The experimental groups (HD and Tx) had decreased ratios of ApoAI/ApoCIII and increased ratios of ApoCIII non B.

The HD patients also had increased ApoE:ApoB and ApoCIII:B ratios suggesting the existence of compositional apolipoprotein changes. There is considerable indirect evidence that post-transplant hyperlipidemia may have a significant effect on the progression of chronic rejection to the renal graft (6). Studies indicate that triglyceride-rich lipoprotein may be more linked to graft dysfunction than cholesterol-rich lipoprotein.

CONCLUSIONS

Both groups of investigated patients have abnormal serum lipids and lipoproteins profile. Moreover, disturbances were more intensive in HD patients in comparison with patients after renal transplantation. Increased levels of CIII and E containing ApoB in HD patients suggest qualitative changes in the composition of lipoprotein particles resulting largely from impaired catabolism. We found a significant inverse correlation between the time which passed from executed kidney transplantation and CIII:B, ratio which means diminished risk ascertained. Dyslipoproteinemia belongs to basic factors of risk of cardio-vascular complications and other vascular complication in this population.

REFERENCES

1. Attman P. O. et al.: Dialysis modalities and dyslipidemia. Kidney Int., 63, 110, 2003.
2. Brown J. H. et al.: Influence of immunosuppressive therapy on lipoprotein (a) and other lipoproteins following renal transplantation. Nefron, 75, 277, 1997.
3. Chan M. K., Varghes Z. et al.: Lipid abnormalities in uremia, dialysis and transplantation. Kidney Int., 19, 625, 1981.
4. Drucke T. B., Abdulmassih Z. et al.: Atherosclerosis and lipid disorders after renal transplantation. Kidney Int., 39, 24, 1991
5. Freedman D. S., Srinivasan S. R. et al.: Divergent levels of high-density lipoprotein cholesterol and apolipoprotein A1 in children. Arteriosclerosis, 7, 347, 1987.
6. Guijarro C., Massry Z. A., Kasiske B. L.: Clinical correlation between renal allograft failure and hyperlipidemia. Kidney Int., 48 (suppl. 52), 56, 1995.
7. Harris K. P. G. et al.: Alterations in lipid and carbohydrate metabolism due to cyclosporine A in renal transplant recipients, Br. Med. J., 292, 6, 1986.
8. Kasiske B. L., Guijarro C. et al.: Cardiovascular disease after renal transplantation. J. Am. Soc. Nephrol., 7, 158, 1996.
9. Kasiske B. L.: Hyperlipidemia in patients with chronic renal disease. Am. J. Kidney Dis., 32 (suppl. 3), 142, 1998.
10. Massry Z. A. et al.: Chronic renal allograft rejection: Immunologic and nonimmunologic risk factors. Kidney Int., 49, 518, 1996.
11. Ponticelli C. et al.: Lipid disorders in renal transplant recipients. Nephron , 20, 189, 1978.
12. Prinsen B. H. C. et al.: Hypertriglyceridemia in patients with chronic renal failure: possible mechanism. Kidney Int., 63, 121, 2003.
13. Shoji T., Nishizawa Y. et al.: Impaired metabolism of high-density lipoprotein in uremic patients. Kidney Int., 41, 1653, 1992.
14. Teplan V. et al.: Hyperlipidemia after renal transplantation and effect of individualized therapy. Adv. Clin. Exp. Med., 7, 119, 1998.

15. Toto R. D., Vega G. L. et al.: Mechanism and treatment of dyslipidemia of renal disease. Curr. Opin. Nephr. Hyperten., 2, 784, 1993.

SUMMARY

The aim of the study was to evaluate the serum lipid and apolipoprotein profiles among patients after renal transplantation (Tx) and to compare them with the profiles obtained for permanently hemodialysed patients (HD). The investigations were performed at 15 Tx, 40 HD patients and the control group of 40 healthy subjects. There were significantly increased TG, ApoAIII, ApoE, TC/HDL-C, ApoCIII non B, ApoCIII:B and decreased HDL-C, ApoAI, HDL-C/ApoAI, ApoAI/ApoCIII, ApoB/ApoCIII ratios comparing HD patients to the control group. There were increased TG, ApoCIII, ApoCIII non B, ApoB/ApoCIII ratios and decreased ApoAI/ApoCIII ratios in Tx patients as compared to the control subjects. Moreover, there were significantly higher HDL, ApoAI, HDL/ApoAI, ApoCIII non B and lower ApoE, ApoE/ApoB, ApoCIII:B ratios in Tx patients as compared to these of HD patients. Significant inverse correlation of the time which passed from executed Tx and ApoCIII:B ratio ($r = -0.67$; $p < 0.01$) at renal transplant patients were observed, which means the diminished risk of development of atherosclerosis.

Zaburzenia gospodarki lipidowej i apolipoproteinowej (ApoAI, ApoB, ApoCIII, ApoE) u pacjentów po transplantacji nerek (Tx) i pacjentów przewlekle hemodializowanych (HD)

Celem naszej pracy była ocena profilu lipidowego i apolipoproteinowego u pacjentów Tx w porównaniu z pacjentami HD. Badania przeprowadzono u 15 pacjentów Tx, 40 pacjentów HD oraz u 40 osób zdrowych stanowiących grupę kontrolną. W przeprowadzonych badaniach stwierdzono, że w grupie pacjentów HD pojawiła się dyslipoproteinemia, która manifestuje się istotnym wzrostem TG, ApoAIII, ApoE oraz wskaźników TC/HDL-C, ApoCIII nie B, ApoB:ApoCIII, ApoAI, HDL-C/ApoAI, ApoAI/ApoCIII i ApoB/ApoCIII, oraz spadkiem HDL-C w porównaniu z grupą kontrolną. Stwierdzono także istotny wzrost TG, ApoCIII, wskaźników ApoCIII nie B, ApoB/ApoCIII i znamienny spadek ApoAI/ApoCIII u pacjentów Tx w porównaniu z grupą kontrolną. Ponadto wykazano znamienny wzrost HDL-C, ApoAI, wskaźników ApoCIII nie B i istotny spadek ApoE, ApoE/ApoB, ApoB:CIII u pacjentów Tx w porównaniu z pacjentami HD. U pacjentów Tx stwierdzono obecność ujemnej korelacji pomiędzy wskaźnikiem ApoCIII:B a czasem po wykonanej transplantacji ($r = -0.67$; $p < 0.01$) co oznacza, że pacjenci Tx są w mniejszym stopniu narażeni na rozwój miażdżycy naczyń.