ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN – POLONIA
VOL. XXIII, N 2, 20 SECTIO DDD 2010

[1]Department of Laboratory Diagnostics,
[2]Department of Nephrology, Medical University of Lublin

ELŻBIETA KIMAK[1], MAGDALENA HAŁABIŚ[1], IWONA BARANOWICZ-GĄSZCZYK[2], JANUSZ SOLSKI[1], ANDRZEJ KSIĄŻEK[2]

Serum lipid and lipoprotein concentrations treated and non-treated with statins in post-renal transplant patient (Tx)

Stężenie lipidów i lipoprotein w surowicy krwi pacjentów po transplantacji nerki leczonych i nieleczonych statynami

INTRODUCTION

Post-renal transplant patients (Tx) with hyperlipidemia had an increased risk of atherosclerosis. Tx patients had preexisted cardiovascular disease at the time of transplantation. Immunosuppresive therapy promotes development of new risk factors, notably hyperlipidemia and hypertension or glucose intolerance [1, 2]. A multivariate analysis of renal transplant patients revealed significantly increased hazard ratios for patients death due to cardiovascular disease among patients with hyperlipidemia, while hyperlipidemia and low levels of HDL-C were independent risk factors for graft failure [7, 9–13]. Thus renal transplant recipients with hyperlipidemia are at increased risk of the atherosclerotic vascular disease [7, 17]. The statins has been shown to be effective in lowering hyperlipidemia and a reduced cardiovascular risk in the general population [17]. Lipid management in kidney transplant patients is important to improve the outcome after successful transplantation and to minimize the occurrence of CVD. Although hyperlipidemia could be treated by modifying immunosuppressant protocol, the use of statins and a proper low-fat diet elevated lipid concentrations still remain a concern [4–5, 9]. The present study examined clinical and routine laboratory parameters and lipids, lipoproteins and lipid and lipoproteins ratios in Tx patients treated and non-treated with statins.

MATERIAL AND METHODS

We studied 20 post-renal transplant recipients (male and female) at the age between 21–60 and the reference group. The reference group consisted of 30 subjects chosen from among apparently normolipidemic healthy individuals. The study was conducted in accordance with the guidelines of the Ethics Committee, Medical University of Lublin. The studied patients were without active inflammatory disease, liver disease, malignancy, diabetes mellitus and they did not smoke. The causes

of renal insufficiency in post-renal transplant patients were: 11 glomerulonephritis, 5 interstitial nephritis, 2 polycystic disease, 2 hypertensive nephrosclerosis. The post renal transplant patients received cyclosporine A (CsA) + prednisone (n=13), tacrolimus + prednisone (n=7) and atorvastatine or simvastatine (n=10). They received a low dose of statins. Tx patients (n=20) were divided into 2 groups: Tx patients with (n=10) and without (n=10) statins therapy

Lipids, lipoproteins, routine laboratory parameters were obtained in the serum after 14-hour overnight fasting. Blood was taken from veins into commercial tubes. The serum was immediately separated and stored in aliquots at -80^0C until use. Routine laboratory parameters (the levels of urea, uric acid, creatinine, total protein, albumin) and lipids and lipoproteins (apoA, apoB) were determined on Hitachi 902 analyzer, and hemoglobin using ADVIA analyser, Bayer, as previously described [9–13]. LDL-cholesterol (LDL-C) was calculated according to the Friedewald formula [3]. Non-HDL-cholesterol (non-HDL-C) was calculated as total cholesterol (TC) minus HDL-C.

Statistical analysis was performed using one-way analysis of the ANOVA variance and multiple comparisons for assessment of the mean ± standard deviation (SD) in post-renal transplant patients and compared to the reference group. The data were expressed as mean standard deviation and values of $p<0.05$ were considered significant. Statistical analysis was performed using the STATISTICA program (StatSoft, Krakow, Poland).

RESULTS

Tx patients with statins therapy showed worse clinical and laboratory parameters (table 1).

Table 1. Clinical and laboratory parameters in Tx patients with and without stains therapy and the reference group

	Tx patients with statins therapy n=10	Tx patients without statins therapy n=10	Reference group n=30
Age (years)	47 ± 11	39 ± 10	38 ± 14
BMI kg/m^2	25.1 ± 2.0	24.2 ± 1.5	23.2 ± 1.5
Urea mg/dl	57.00 ± 26.18**	52.38 ± 31.73**	17.8 ± 12.6
Creatinine mg/dl	1.69 ± 0.88**	1.59 ± 0.65**	0.80 ± 0.20
Total protein g/dl	7.18 ± 0.66	7.28 ± 0.48	7.20 ± 0.30
Albumin g/dl	4.19 ± 0.37	4.29 ± 0.27	4.30 ± 0.40
Hemoglobin mg/dl	13.20 ± 1.41	14.10 ± 1.27	14.70 ± 1.60
GFR	53.9 ± 18.2***	65.39 ± 15.90**	117.5 ± 12.3
Time after transpl.	53.31 ± 35.9o	40.9 ± 32.1	

$P<0.05^{*}$ $p<0.01^{**}$ $p< 0.001^{***}$

The results indicated that Tx patients with statins therapy had a significantly higher concentration of TG, non-HDL-C and TG/HDL-C, TC/HDL-C ratio, and a lower concentration of HDL-C, and apoAI/apoB, HDL-C/apoAI ratios than Tx patients without statins therapy. However, the concentrations of TC, LDL-C and apoB were simile in both studied group. Moreover, in both concentrations of TG, non-HDL-C and TC/HDL-C, LDL-C/HDL-C, TG/HDL-C ratios were significantly increased, but HDL-C

level and apoAI/apoB, HDL-C/apoAI ratios were decreased in comparison to the reference group

Table 2. Lipid and lipoprotein profiles in Tx patients with and without statins therapy and the reference group

	Tx patients with statins therapy n=10	Tx patients without statins therapy n=10	Reference group n=30
TG mg/dl	202.87±55.30+***	166.60±51.50***	86.78 ± 26.71
TC mg/dl	205.00±31.30	206.00±25.96	177.50 ± 28.03
LDL-C g/dl	131.75±25.82	124.67±22.34	99. 92 ± 24.42
HDL-C mg/dl	32.64±4.44***	46.84±8.30**	57.71 ± 8.41
non-HDL-C mg/dl	172.23±31.43+***	157.08±25.0**	117.29 ± 24.89
ApoA1 mg/dl	141.42±8.19*	159.03±13.6	162.10 ± 10.55
ApoB mg/dl	91.42±21.29	88.30±16.90	79.90 ± 15.63
ApoAI/apoB	1.62±0.33**	1.90±0.39*	2.14 ± 0.38
HDL-C/apoAI	0.23±0.029+***	0.28±0.031**	0.37 ± 0.04
TC/HDL-C	6.29±1.31+***	4.52±0.79**	2.96 ± 0.56
LDL-C/HDL-C	3.98±1.08**	2.76±0.65**	1.64 ± 0.47
TG/HDL-C	6.53±2,06+***	3.72±1.39**	1.43 ± 0.50

$p< 0.05^{*}$ $p< 0.01^{**}$ $p< 0.001^{***}$

DISCUSSION

Cardiovascular diseases (CVDs), including acute myocardial infarction, cardiac arrhytmias, heart failure and stroke, have become the leading cause of mortality in renal transplant recipients, accounting for over 50% of deaths in these patients. In post-renal transplant patients lipid abnormalities appear to progress in a large fraction of patients. The typical pattern includes marked hypercholesterolemia and hypertriglyceridemia as the consequence of immunosuppressive therapy [1, 2, 7, 9]. Immunosuppressive therapy is the main factor that influences the posttransplant lipidemic profile. Corticosteroids, CSA, TAC (to a lesser degree than CSA) increase the posttransplant cholesterol and triglyceride levels, usually in a dose-dependent fashion [1, 2]. Previously, we showed that the post-renal transplant patients with dyslipidemia had elevated both the mass of cholesterol (non-HDL-C) and apoB (number of atherogenic particles) in apoB-containing lipoproteins (TRL). Moreover, post-renal transplant patients with normolipidemia had a normal mass of cholesterol (non-HDL-C) and apoB, but they had elevated TRL (apoB:C) and a decreased apoAI/CIII ratio. These results suggest disturbed lipoprotein metabolism in normolipidemic post-renal transplant patients (small dense LDL and small dense HDL) [10]. Our study clearly shows that TRL and lipid and lipoprotein ratios are very sensitive markers of early dyslipidemia in post renal transplant patients [9–13]. These studies indicated that both triglyceridemia and a decrease HDL-C concentration are very important risk factors of chronic allograft failure and atherosclerosis in post-renal transplant patients. However, oxidative stress and reduced antioxidant capacity of HDL are negative risk factors associated with chronic renal allograft failure and atherosclerosis in post-renal transplant patients [9–13].

Our present study showed that post-renal transplant patients received prednisone and cyclosporine A, and prednisone and tacrolimus with statins therapy had hipertriglyceridemia and

higher concentration of non-HDL-C and lipid ratios and lower HDL-C, apoAI levels and lipoprotein ratios (apoAI/apoB, HDL-C/apoAI) than Tx patients without stains therapy. Moreover, Tx patients with higher dyslipidemia and with statins therapy had poorer clinical and laboratory parameters and they had a high risk for developing cardiovascular disease as well as recipients with pre-existing disease, which leads to allograft dysfunction and subsequent rejection. We suggest that non-HDL cholesterol should always be measured in the setting or premature myocardial infarction as an additional estimation of this risk in post-renal transplant patients [7, 9–15]. The efficacy of statins for the prevention of cardiovascular events is well established in the general population but remains unknown in renal transplant recipients [15]. Kidney transplantation reduces mortality and cardiovascular deaths, more so than dialysis, although survival for both remains worse than in non-renal disease populations. This may be for reasons of preexisting cardiovascular disease acquired during renal progression or dialysis; however, recent population data suggest that even minor kidney dysfunction (which is almost universal in graft recipients) is associated with an increased cardiovascular risk [15]. In addition to reduction in the risk of ischemic heart disease and favorable effects on patient and graft survival, improvement in renal transplant function has also been reported [5]. Statins as antilipidemic agents have plejotropic effects including those on renal function in renal allograft recipients [7, 17]. We showed that Tx patients with low dose statins therapy had a favourable role on lipid and lipoprotein concentrations and lipid and lipoprotein ratios. Although the concentration of TG, non-HDL-C and lipid ratios were worse than the reference group, total cholesterol and LDL-cholesterol levels were non-significantly increased in studied patients. HDL-C has been demonstrated to be a strong, independent, and inverse predictor of coronary heart disease risk and therefore has emerged as a potential therapeutic target [4–6] but statins therapy has not improved it. Recently, it was reported that the concentration and distribution of LDL and HDL subfraction may be a more sensitive indicator of coronary heart disease and renal allograft reject risk than total cholesterol, LDL-C or HDL-C levels [4, 8, 14].

CONCLUSIONS

A variety of immunosuppressive therapies in Tx patients are seen to be one of the main factors that influence post-renal transplant abnormal lipid and lipoprotein profiles. The statins therapy demonstrate the favourable role on the concentration of total cholesterol and LDL-cholesterol but a minor role on triglyceride and HDL-cholesterol levels, and it can prevent progression of atherosclerosis and chronic allograft failure in Tx patients. However, future studies are required.

REFERENCES

1. Fellstrom B., Holdaas H., Jardine A.: Cardiovascular Disease in Renal Transplantation: Management by Statins. Transplant. Rev., 18, 122, 2004.
2. Fellstrom B., Jardine A.G., Soveri I. et al: Renal dysfunction is a strong and independent risk factor for mortality and cardiovascular complications in renal transplantation. Am. J. Tranplant., 5, 1986, 2005.
3. Friedewald W.T., Levy R.I., Frierickson D.S.: Estimation of the concentration of low-density lipoprotein

cholesterol in plasma without the use of the preparative ultracentrifuge. Clin. Chem., 18, 499, 1972.
4. Harngi M., Mirdamadi H., Seres I. et al: Atorvastatin effect on the distribution of high-density lipoprotein subfractions and human paraoxonase. Transplant. Res., 153, 190, 2009.
5. Hariparshad S.P., Madala N.D., Assounga A.G.H.: Statin therapy ameliorates renal allograft function. Transplant. Proc., 41, 4178, 2009.
6. Jones P.H., Hunninghake D.B., Ferdinand K.C., et al.: Effects of rosuvastatin versus atorvastatin, simvastatin, and pravastatin on non-high-density lipoprotein cholesterol, apolipoproteins, and lipid ratios in patients with hypercholesterolemia: additional results from the STELLAR trial. Clin. Ther., 26, 1388, 2004.
7. Kasiske B.L., Cakkera H.A., Roel J.: Explained and unexplained ischemic heart disease risk after renal transplantation. J. Am. Soc. Nephrol., 11, 1735, 2000.
8. Kawano M., Nagasaka S. et al.: Pitavastatin decreases plasma prebeta1-HDL concentration and might promote its disappearance rate in hypercholesterolemic patients. J. Atheroscler. Thromb., 15, 41, 2008.
9. Kimak E., Hałabiś M.: Serum hypertriglyceridemia as an important risk factor of chronic allograft failure in post-renal transplant patients. Annales UMCS, Sect. DDD, 22, 115, 2009.
10. Kimak E., Książek A. et al.: Disturbed lipids, lipoproteins and triglyceride rich-lipoproteins as well as fasting and nonfasting non-high–density lipoprotein cholesterol in post-renal transplant patients. Ren. Fail., 29, 705, 2007.
11. Kimak E., Solski J. et al: Serum lipid, leptin, parameters of oxidative stress and PON-1 activity in post-renal transplant patients. Annales UMCS. Sect. DDD, 21, 355, 2008.
12. Kimak E., Hałabiś M., Baranowicz-Gąszczyk I.: Relationships between serum lipid, lipoprotein, triglyceride-rich lipoprotein, and high-density lipoprotein particle concentrations in post-renal transplant patients. JZUS-B, 11, 249, 2010.
13. Kimak E., Książek A., Solski J.: Disturbed lipoprotein composition in non-dialyzed, hemodialysis, continuous ambulatory peritoneal dialysis and post-transplant patients with chronic renal failure. Clinical Chemistry and Laboratory Medicine, 44, 64, 2006.
14. Moren X., Deakin SP., Liu M.L. et al: HDL subfraction distribution of paraoxonase-1 and its relevance to enzyme activity and resistance to oxidative stress. J. Lipid Res., 49, 1246, 2008.
15. Ritz E., Wanner C.: Statin use prolongs patients survival after renal transplantation. J. Am. Soc. Nephrol., 19, 2035, 2009.
16. See V.Y., De Nofrio D., Goldberg L. et al.: Effect of atorvastatin on post cardiac transplant increase in low-density lipoprotein cholesterol reduces development of intima hyperplasia and progression of endothelial dysfunction. Am. J. Cardiol., 92, 11, 2003.
17. Takumoto T., Tanabe K., Ishida H. et al.: Impact of Fluvastatin on Hyperlipidemia after Renal Transplantation. Transplant. Proc., 36, 2141, 2004.
18. Tory R., Sachs-Barrable K., Goshko C.B. et al: Tacrolimus-Induced Elevation in Plasma Triglyceride Concentration after Administration to renal Transplant Patients in Partially Due to a Decrease in Lipoprotein Lipase Activity and Plasma Concentration. Transplantation, 1, 62, 2009.
19. Wiesbauer F., Heinze G., Mitterbauer C. et al: Statin use is associated with prolonged survival of renal transplant recipients. J. Am. Soc. Nephrol., 19, 2211, 2008.

SUMMARY

Cardiovascular diseases (CVDs), including acute myocardial infarction, cardiac arrhytmias, heart failure and stroke have become the leading cause of mortality in renal transplant recipients, accounting for over 50% of deaths in these patients. The studies were performed in 20 renal transplant patients (Tx) (male and female) at the age between 21–60 years and the reference group. Tx patients were without an active inflammatory disease, liver disease, malignancy, or diabetes mellitus, and they were not smokers. Seventeen patients had hypertension. The causes of renal insufficiency in the post-renal transplant (Tx) patients were: 11 glomerulonephritis, 5 interstitial nephritis, 2 polycystic disease, 2 hypertensive nephrosclerosis. The post-renal transplant patients received cyclosporine A (CsA) + prednisone (n=13), tacrolimus + prednisone (n=7) and atrovastatine or simvastatine (n=10). They received a low dose of statins. Tx patients (n=20) were divided into 2 groups: Tx patients with (n=10) and without statins therapy (n=10). The present study examined clinical and routine laboratory parameters and lipids, lipoproteins and lipid and lipoproteins ratios in Tx patients treated and non-treated with statins. Lipids, lipoproteins, routine laboratory parameters were obtained in the serum after 14-hour overnight fasting. Routine laboratory parameters (the level of urea, uric acid, creatinine, total protein, albumin) and lipids and lipoproteins (apoA, apoB) were determined on Hitachi 902 analyzer, and hemoglobin using ADVIA analyser, Bayer. LDL-cholesterol (LDL-C) was calculated according to the Friedewald formula. Non-HDL-cholesterol (non-HDL-C) was calculated as total cholesterol (TC) minus HDL-C. The obtained results in Tx patients with statins therapy shows worse clinical and laboratory parameters. The results indicated that Tx patients with statins therapy had a significantly higher concentration of TG, non-HDL-C and TC/HDL-C, TG/HDL-C ratios, and a lower concentration of HDL-C, and apoAI/apoB, HDL-C/apoAI ratios than Tx patients without statins therapy. However, the concentrations TC, LDL-C and apoB were simile in both studied group. Moreover, in both concentrations of TG, non-HDL-C and TC/HDL-C, LDL-C/HDL-C, TG/HDL-C ratios were significantly increased, but HDL-C level and apoAI/apoB, HDL-C/apoAI ratios were decreased in comparison to the reference group. A variety of immunosuppressive therapies in Tx patients are seen to be one of the main factors that influence post-renal transplant abnormal lipid and lipoprotein profiles. The statins therapy demonstrate a favourable effect on the concentration of total cholesterol and LDL-cholesterol but a minor role in triglyceride and HDL-cholesterol levels. Statins can prevent progression of atherosclerosis and chronic allograft failure in Tx patients. However, future studies are required.

Keywords: lipids, lipoproteins, statins, post-renal transplant patients.

STRESZCZENIE

Choroby sercowo-naczyniowe są przyczyną wysokiej śmiertelności pacjentów po transplantacji nerki, ponieważ ponad 50% tych chorych umiera. Badania wykonano u 20 pacjentów po transplantacji nerki (Tx) (mężczyzn i kobiet) w wieku 21–60 lat i w grupie referencyjnej. Tx pacjenci nie cierpieli na choroby zapalne, choroby wątroby, nowotwory, cukrzycę i nie palili tytoniu. Natomiast 17 pacjentów miało nadciśnienie. Przyczyną niewydolności nerek u tych chorych było: 11 – *glomerulonephritis*,

5 – *interstitial nephritis*, 2 – *polycistic*, 2 – *hypertensive nephrosclerosis*. Pacjentom Tx podawano cyklosporynę A (CsA) + prednison (n=13), tacrolimud + prednison (n=7) i atorwastatynę albo simwastatynę (n=10). Pacjenci otrzymywali niskie dawki statyn. Pacjenci Tx (n=20) byli podzieleni na dwie grupy: Tx leczonych (n=10) i Tx nieleczonych (n=10) statynami. Celem badań było oznaczenie klinicznych i laboratoryjnych parametrów oraz lipidów, lipoprotein i wskaźników lipidowych i lipoproteinowych u pacjentów Tx leczonych i nieleczonych statynami. Lipidy, lipoproteidy i rutynowe laboratoryjne parametry były oznaczane w surowicy krwi po 14-godzinnym głodzeniu. Rutynowe laboratoryjne parametry (poziom mocznika, kreatyniny, białka całkowitego, albuminy), lipidów i lipoprotein (apoAI, apoB) były oznaczane na analizatorze Hitachi 902, a hemoglobina przy użyciu analizatora ADVIA, Bayer. Stężenie LDL-C było wyliczane z wzoru Friedewalda. Cholesterol zawarty poza frakcją HDL (non-HDL-C) wyliczono z różnicy cholesterolu całkowitego i HDL-C. Wyniki pacjentów Tx leczonych statynami wykazały gorsze kliniczne i laboratoryjne parametry. Pacjenci Tx leczeni statynami mieli istotnie wyższe stężenie TG, nie-HDL-C i wartości wskaźników TC/HDL-C, TG/HDL-C oraz niższe stężenie HDL-C, apoAI i wartości wskaźników apoAI/apoB, HDL-C/apoAI od pacjentów Tx nieleczonych statynami. Stężenie TC, LDL-C i apoB było podobne w obu badanych grupach. Jednakże w obu grupach stężenie TG, nie-HDL-C i wartości wskaźników TC/HDL-C, LDL-C/HDL-C, TG/HDL-C były istotnie wyższe, a stężenie HDL-C i wartości wskaźników apoAI/apoB, HDL-C/apoAI były istotnie niższe w porównaniu z grupą referencyjną. Immunosupresyjne leczenie stosowane u pacjentów po transplantacji nerki jest jednym z głównych czynników, które wpływają na nieprawidłowy profil lipidowy i lipoproteinowy u tych chorych. Natomiast statyny wywierają korzystny wpływ na poziom cholesterolu całkowitego i LDL-cholesterolu oraz mniej korzystny na poziom TG i HDL-cholesterolu. Statyny mogą powstrzymywać progresję miażdżycy i przewlekłe odrzucanie przeszczepu. Jednakże wymagane są dalsze badania.

Słowa klucze: lipidy, lipoproteiny, statyny, pacjenci po transplantacji nerki.