ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN – POLONIA
VOL. XXIV, N 1, 5 SECTIO DDD 2011

[1]Department of Laboratory Diagnostic, Medical University of Lublin, Poland
[2]Department of Clinical Nephrology, Medical University of Lublin, Poland

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

# *Serum lipids, lipoproteins, oxidative stress parameters and paraoxonase 1 (PON-1) activity in post-renal transplant patients (Tx) with stable renal function and Tx patients without and with statins therapy*

Lipidy, lipoproteiny, parametry stresu oksydacyjnego i aktywność paraoksonazy 1 (PON-1) w surowicy krwi pacjentów po transplantacji nerki ze stabilną funkcją nerki, po i bez leczenia statynami

## INTRODUCTION

Cardiovascular risk factors such as hypertension, and post-renal transplantation diabetes mellitus and genetic predisposition to hyperlipidemia, obesity, and anti-hypertension medications are factors for dyslipidemia in this population [4]. Posttransplant dyslipidemia occurs in at least 60% of patients after renal transplantation. In the face of hyperlipidemia, the impact of an episode of acute rejection is more severe than in transplant recipients with normal lipid profiles [39]. In renal transplantation there is an imbalance between the reactive oxide species (ROS) and antioxidant mechanisms that results in oxidative stress [33]. Serum paraoxonase (PON-1) is an esterase/lactonase associated with HDL, playing an anti-inflammatory role and causing a protective effect against atherosclerosis and oxidative damage of lipoprotein cells [1,3]. The studies suggest that paraoxonase prevents low-density lipoprotein oxidation by hydrolyzing lipid peroxides [3]. Impaired lipoprotein metabolism was found in uremic patients and post-renal transplant patients and one of the abnormalities was hypertriglyceridemia and decreased HDL cholesterol [15-20]. It is not currently known whether post-renal transplant patients with normal lipid levels and without anti-lipid lowering therapy and receiving immunosuppressive drugs have an impaired antioxidant system.

The aim of the present study was to investigate lipids, lipoproteins, lipid and lipoprotein ratios, leptin, total peroxide (OxyStat) concentrations, and paraoxonase-1 activity (PON-1) in post-renal transplant (Tx) patients with stable renal function and normolipidemia and, in comparison to Tx patients, with and without statins therapy and healthy subjects.

## MATERIAL AND METHODS

Serum levels of lipid, lipoprotein, leptin, total peroxide (OxyStat), and paraoxonase 1 activity (PON-1) were determined in 67 post-renal transplant patients (Tx) and 53 healthy persons as reference group. The post-renal transplant patients received prednisone and cyclosporine A (CSA) and prednisone and prograf (Table1). Tx patients were divided into three groups: Tx patients with normolipidemia and stable renal function (n=11), Tx patients without statins therapy (n=25) and Tx patients with statin therapy (n=31). Tx patients with stable renal function and normolipidemia were without statins therapy and they had favourable clinical and laboratory parameters. Tx patients without statins therapy had moderate hypercholesterolemia and hypertriglyceridemia. Tx patients with statins therapy had hypercholesterolemia and hypertriglyceridemia and they received atorvastatine or simvastatine (Table1). All studied patients were without active inflammatory disease, liver disease, diabetes, malignancy and they did not smoke. Moreover, 32 patients had hypertension. Hypertensive patients were using anti-hypertensive medications of either calcium channel blockers or angiotensin converting enzyme antagonists, blockers AT1 receptors and alpha-blockers, but no diuretics. In each group studied, hypertension occurred in about 50% patients who received from one to four hypertensive drugs. Tx patients with normolipidemia were without cardiac incidence, Tx patients without statins (n=1) and with statins (n=1) therapy had similar cardiac incidences. The control group contained 53 subjects chosen from among apparently normolipidemic with normal blood tension healthy ones (26 women and 27 men, aged from 21 to 50 years). They were without cardiac incidence, renal disease, diabetes, liver disease, active inflammatory disease, malignancy, obesity or glucose intolerance. Healthy subjects in control did not take any medications and smoking or drinking alcohol. The study was carried out in accordance with the guidelines of the Ethics Committee of the Medical University, Lublin.

Lipids, lipoproteins, and routine laboratory parameters were obtained in serum after 14-hour overnight fasting. Blood was taken from veins into commercial tubes. Serum was immediately separated and stored in aliquots at $-80^0$C until use. Routine laboratory parameters (the level of urea, uric acid, creatinine, total protein, albumin) and lipids or lipoproteins (apoA, apoB) were determined on Hitachi 902 analyzer, and haemoglobin using ADVIA analyser, Bayer. Triglycerides (TG) were determined using the standard enzymatic technique (Roche kit). Total cholesterol (TC) was determined by the enzymatic-colorimetric methods (cholesterol CHOD-PAP, Roche), HDL-cholesterol (HDL-C) by the direct method with immunoinhibition, and LDL-cholesterol (LDL-C) was calculated according to the Friedewald formula [5]. Non-HDL-cholesterol (non-HDL-C) was calculated as total cholesterol (TC) minus HDL-C. ApoAI and apoB were measured using the turbidimetric methods (Roche kits).

Serum leptin was measured by the enzyme-linked immunosorbent assay (ELISA) method using DRG, Germany. Paraoxonase-1 was performed in the presence of 2M NaCl (PON-1salt-stimulated activity) and its absence (PON-1basal activity). Paraoxonase-1 activity was determined using 1.2mM paraoxon (*O,O*-diethyl-*O*-p-nitrophenyl phosphate; Sigma Chemical, St. Louis, Mo., USA) as substrate. The PON-1 activity was measured by the modified Fourlong's method [6] from the initial velocity of p-nitrophenol production at $37^o$C, and its increased absorbance at 405 nm was recorded by an autoanalyzer (Cobas-Mira Plus, Roche Diagnostica, Switzerland). Serum was added to basal assay mixture containing

100 mM TRIS-HCL buffer (pH 8.5) with paraoxon, 1mM $CaCl_2$. A PON-1 activity of 1U/L was defined as 1µmol of p-nitrophenol hydrolized per minute. The molar extinction coefficient of p-nitrophenol was 18053 $mol^{-1}$ $cm^{-1}$ . The intra- and inter -assay coefficients of variation were 1.8% and 3.8%, respectively. OxyStat test was used from Biomedica GmbH, Wien. The colorimetric assay of OxyStat measures the total peroxide concentration of a sample, utilizing a quick and simple assay procedure. The results show a direct correlation between free radicals and circulating biological peroxides, allowing thus characterization of the oxidative status in biological samples. The results are expressed in µmol/L. The intra- and inter -assay coefficients of variation were 3.1% and 5.1%, respectively.

Statistical analysis. The data were expressed as medians and minimum-maximum. A statistical analysis of our results was performed utilizing the nonparametric Kruskal-Wallis test for comparison Tx patients with stable renal function and patients with and without statins therapy in relation to the reference group. The statistical significance of all variables was established at $p<0.05$, and statistical analysis was performed using the STATISTICA program (StatSoft, Krakow, Poland).

## RESULTS

Table 1 presents the results of the clinical and laboratory parameters in post-renal transplant patients with stable renal function and normolipdemia and with and without statins therapy and control group. Tx patients with stable renal function and normolipidemia had favourable clinical and laboratory parameters (eGFR, urea, creatinine) than those without and with statins therapy (Table1).

Table 1. Clinical and routine laboratory parameters in control group and post-renal transplant patients (Tx) with stable renal function and normolipidemia and Tx patients with statins and without statins therapy, median(min-max)

| | Control group n=53 | Tx patients with stable renal function and normolipidemia n = 11 | Tx patients without statins n=25 | Tx patients with statins n=31 |
|---|---|---|---|---|
| Age, years | 39(21-50) | 38(27-52) | 48(33-57) | 49(35-62) |
| Sex (male, female) | 27 M, 26 F | 5 M, 6F | 12M, 13F | 16M, 15F |
| BMI kg/$m^2$ | 23(20-25) | 24(21-29) | 24(17-32) | 25(21-33) |
| Time after transplant (months) | - | 38(15-67) | 41(12-79) | 49(13-62) |
| eGFR mL/min/kg | 91.5(74-125) | 78.3(65.0-123) | 67.0(30.0-112) | 59.0(23.0-93.0) |
| Urea, mg/dl | 26.5 ± 6.2 | 35(25-38)** | 49(24-89)** | 45(20-102)** |
| Creatinine, mg/dl | 0.82 ± 0.10 | 1.34(0.80-1.37)** | 1.46(1.00-3.26)** | 1.47(0.99-3.48)** |
| Total protein, mg/dl | 7.25 ± 0.53 | 7.41(6.58-7.87) | 7.31(6.30-8.83) | 7.13(7.20-7.80) |
| Albumin, g/dl | 4.58 ± 0.38 | 4.34(4.08-4.63) | 4.18(3.39-4.90) | 4.16(3.20-4.60) |
| Hemoglobin, mg/dl | 14.12 ± 1.23 | 14.3(12.3-17.2) | 13.4(10.3-17.6) | 13.3(11.1-16.1) |
| Leptin ng/ml | 9.8(2.9-13.5) | 24.0(5.8-54.6)*** | 24.7(5.2-75.0)*** | 25.2(21.7-43.9)*** |
| Statins | | 0 | 0 | 31 |
| Prednisone | | 11 | 25 | 31 |
| Cyclosporine A | | 9 | 17 | 22 |
| Prograf | | 2 | 8 | 9 |

Values are expressed as mean ± SD, BMI: body mass index, M: male, F: female $p < 0.05$-* ; $p< 0.01$-**, $p < 0.001$ - *** - vs control group

The concentrations of lipid and lipoprotein and lipid and lipoprotein ratios in post renal transplant patients with stable renal function and normolipidemia, and without and with statin therapy and control group are shown in Table 2.

Table 2. Lipids, lipoproteins and lipid and lipoprotein ratios, and leptin, total peroxide (OxyStat), and PON-1 activity in control group and post-renal transplant patients (Tx) with stable renal function and normolipidemia and Tx patients with statins and without statins therapy, median (min-max)

| | Control group n = 53 | Tx patients with stable renal function and normolipidemia n=11 | Tx patients without statins n=25 | Tx patients with statins N=31 |
|---|---|---|---|---|
| (TG) mg/dL | 88(59-133) | 106(67-132) | 155(73-177)***¶ | 147(83-325)*** |
| TC mg/dL | 180(126-212) | 181(167-200) | 212(138-245)**¶ | 233(157-285)***¶ |
| LDL-C mg/dL | 98(59-137) | 109(50-125) | 134(86-145)**¶ | 144(98-189)**¶ |
| HDL-C mg/dL | 59(45-68) | 50(44-74) | 44(36-81)* | 49(32-80)* |
| Non-HDL-C mg/dL | 121(65-144) | 122(94-131) | 168(116-169)***¶ | 184(65-198)***¶ |
| apoAI mg/dL | 161(145-178) | 154(115-189) | 145(94-156)* | 149(90-198)* |
| apoB mg/dL | 67(62-103) | 63(56-89) | 84(58-136)*¶ | 86(58-145)*¶ |
| ApoAI/apoB | 2.40(1.85-2.81) | 2.41(1.80-2.90) | 1.72(1.20-2.70)*¶ | 1.73(0.99-2.95)*¶ |
| TC/HDL-C | 3.05(2.85-3.31) | 3.68(2.53-4.70)* | 4.80(2.76-5.07)***¶ | 4.87(3.17-9.08)** |
| LDL-C/HDL-C | 1.66(1.29-3.2) | 2.16(1.28-2.98) | 3.04(1.43-3.99)**¶ | 3.09(1.55-6.30)** |
| TG/HDL-C | 1.43(0.98-2.80) | 2.15(1.18-3.10)* | 3.57(1.62-4.60)***¶ | 3.07(1.17-9.15)*** |
| HDL-C/apoAI | 0.37(0.32-0.39) | 0.33(0.29-0.38)* | 0.30(0.28-0.34)** | 0.29(0.27-0.37)** |
| Leptin ng/ml Median(min-max) | 9.8(2.9-13.5) | 24.0(5.8-54.6)*** | 24.7(5.2-75)*** | 25.2(21.7-43.9)*** |
| OxyStat µmol/L Median(min-max) | 135(43-440) | 135.5(45-529) | 238(15-798)*¶ | 214(42-631)*¶ |
| PON1 basal IU/L Median(min-max) | 131(57-469) | 103(66-196)* | 109(53-491)* | 133(52-298) |
| PON1 salt stimul. IU/L Median(min-max) | 233(89-980) | 169(111-393) | 205(97-810) | 220(73-575) |

Values are expressed as mean ± SD, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, Apo: Apolipoprotein, p< 0.05- * ; p< 0.01- ** ; p< 0.001-*** - vs control group; p< 0.05-¶ - vs. Tx patient with stable renal function and normolipidemia

Tx patients with stable renal function and normolipidemia had moderately increased TC/HDL-C and TG/HDL-C ratios and moderately decreased HDL-C/apoAI ratio in comparison to control. Tx patients without statins therapy had significantly increased concentrations of TG, TC, LDL-C, nonHDL-C, apoB and lipid ratios (TC/HDL-C, LDL-C/HDL-C, TG/HDL-C), and decreased HDL-C and apoAI levels and lipoprotein ratios (apoAI/apoB, HDL-C/apoAI) in comparison to control and Tx patients with stable renal function and normolipidemia. Tx patients with statins therapy had significantly increased concentration of lipids (TG, TC, LDL-C, nonHDL-C) and apoB and lipid ratios (TC/HDL-C, LDL-C/HDL-C, TG/HDL-C), and decreased HDL-C and apoAI levels and apoAI/apoB and HDL-C/apoAI ratios in comparison with control and Tx patients with stable

renal function and normolipidemia. These disturbances clearly characterized dyslipidemia in post-renal transplant patients. Tx patients with stable renal function and normolipidemia had increased leptin level and decreased PON-1 activity. Tx patients without statins therapy had increased leptin, OxyStat concentrations and PON-1 activity decreased. However, Tx patients with statins therapy had favourable OxySat level and PON-1 activity in comparison to Tx patients without statin therapy and stable renal function.

## DISCUSSION

Cardiovascular disease is the most important cause of morbidity and mortality as well as an important factor in chronic rejection in renal transplant recipients. It is mediated by various factors that produce accelerated atheromatosis, development of structural heart abnormalities and left ventricular dysfunction [22].

Our results showed that Tx patients with normolipidemia and stable renal function had favourable clinical and laboratory parameters and lipid and lipoprotein profiles than both groups without and with statins therapy**.** Dyslipidemia in Tx patients was characterized by hypercholesterolemia and hypertriglyceridemia and increased triglyceride-rich lipoprotein (TRLs) concentration as indicated by TG and non-HDL-C levels and lipid and lipoprotein ratios [15-20,39]. We showed that Tx patients with stable renal function and normolipidemia had increased TC/HDL-C and TG/HDL-C ratios and decreased HDL-C/apoAI ratios. These disturbances indicated that all Tx patients had disturbed concentration and composition of lipoprotein, and TRLs and HDL metabolism. However, in Tx patients with stable renal function and normolipidemia these disturbances were weakly marked. Moreover, increased concentration of TG, non-HDL-C as TRLs, and TC/HDL-C, LDL-C/HDL-C, TG/HDL-C ratios and decreased HDL-C, apoAI levels and apoAI/apoB, HDL-C/apoAI ratios suggest disturbed HDL subclass distribution because HDL particles tend to become smaller in size. Disturbances in TRLs metabolism are also known to exert impact on HDL-apoAI metabolism [2,11,20,26,32,34]. Triglyceride-enriched HDL (increased TG/HDL-C ratio), generated by increased neutral lipid exchange with triglyceride-rich VLDL, is a preferred substrate for hepatic lipase, which accelerates the catabolism of these thermodynamically unstable HDL particles [2,11]. The TG/HDL-C ratio was an important marker of abnormal TG metabolism, which might provide valuable additional information about the atherogenic potential of lipid profiles. The authors also suggested that elevated TG levels favored the reduction of large-sized HDL particles and generation of small-sized HDL particles [8,11,20,40].

Our results indicated that VLDL, IDL, LDL and HDL particles were smaller, dense and more susceptible to modification and oxidation. They were exposed on oxidative stress, and the anti-oxidative role of PON-1 was weakened. However, Tx patients with statins therapy had lower OxyStat concentration and higher PON-1 basal and salt stimulation activity than Tx patients without statins therapy and with stable renal function (normolipidemia). Our Tx patients received CSA and prednisone or tacrolimus (TAC) and prednisone [23]. The underlying mechanisms of hypertriglyceridemia in transplant patients have not been fully clarified and may indeed be multifactorial. Several immunosuppressive agents including cyclosporine A (CSA), corticosteroids, and TAC appear to play

a significant pathogenic role. Moreover, it was suggested that CSA administration may decrease the antioxidant capacity of renal tissue [7]. Immunosuppressive therapy seems to be the main factor that influences the posttransplant lipidemic profile. Corticosteroids, CSA, TAC (to a lesser degree than CSA) and, in particular, rapamycin increase the posttransplant cholesterol and triglyceride levels, usually in a dose-dependent fashion [4,10,23,28,29,33]. Cyclosporine plays an independent role in elevation of cholesterol levels by modulating the low-density lipoprotein (LDL) receptor. Although the immunosuppressive therapy is strongly related to posttransplant hyperlipidemia its role has not been sufficiently elucidated. Corticosteroides may increase the synthesis of triglycerides by potentiating insulin action at the hepatocyte level or by stimulating enzyme activity that releases stored triglycerides as free fatty acids. Immunosuppressive therapy may have a non-direct effect in triglyceride metabolism in patients with posttransplant stable renal function. A stable renal function may contribute to improved triglyceride metabolism [10,23,28,29], but TAC might have a less profound effect on plasma cholesterol concentrations than CSA. TAC therapy may cause hypertriglyceridemia in a similar manner as CSA therapy. The reduction in lipoprotein lipase (LPL) activity, partly due to the decrease of plasma LPL concentration after TAC administration may be an explanation for hypertriglyceridemia observed in patients administered TAC [37]. However, the study provides strong evidence that TAC is significantly associated with improved free radical metabolism [28,29]. Recently, it was shown that triglyceride-rich lipoproteins (TRLs) lypolysis products provide a pro-inflammatory stimulus that can alter the endothelial barrier function. TRLs lipolysis releases neutral and oxidized FFAs that induce endothelial cell inflammation. Therefore, the oxidative metabolism of FFA in endothelial cells can produce inflammatory responses, and TRLs lipolysis can also release mediators of oxidative stress that may influence the endothelial cell function in vivo by stimulating intracellular reactive oxygen species (ROS) production [25]. Moreover, it was suggested that CSA administration may decrease the antioxidant capacity of renal tissue. More studies on evaluation of the protective effects of antioxidant therapy against CSA nephrotoxicity are underway. The mechanisms of this toxicity are not fully understood, but they are probably associated with increased production of oxygen-free radicals and oxidative stress. Some studies have demonstrated a possible role of oxygen-free radicals in CSA toxicity [7]. $F_2$ –isoprostanes are associated with lipids, although their distribution in human plasma lipoproteins is unknown. Paraoxonase 1 activity was associated with $HDL_2$ and may be a contributing factor to the lower $F_2$-isoprostanes in $HDL_2$ compared with $HDL_3$ [31]. Recently, Jurek et al. [12] reported decreased ability of HDL to suppress expression of VCAM-1 in endothelial cells, and the uptake of oxidized LDL by macrophages can be one of the risk factors for atherosclerosis development in patients with renal failure [12].

Several clinical studies proved the favourable effect of statins not only on serum lipid lowering, but also on HDL-associated human paraoxonase-1 activity in hyperlipidaemic patients. Statins effect on paraoxonase activity seems to be independent of HDL-C elevation [21]. All the statins were able to increase serum paraoxonase activity and decrease triglyceride levels, however, more significant by in patients with AB+BB PON-1 phenotype. The apoB-lowering effect of atorvastatine was also found to be PON-1phenotype dependent. The PON-1 phenotype may be a novel predictive factor for the effectiveness of statins treatment on PON-1 activity and serum lipid levels; however, different types of statins may exert different effects on these parameters [21]. Atorvastatin may influence

the composition and function of HDL, possibly increasing thereby the activity of paraoxonase and preventing atherosclerosis [14]. Atorvastatin alters the HDL subfractions, which may improve its antiatherogenic effect via enhancement of the PON-1 activity [9]. Statins therapy not only decreases the level of LDL-C but also increases the antioxidant activity of PON. Both effects result in a marked reduction in the number of circulating oxidized LDL-C particles which play a major role in the development of atherosclerosis. Therefore, atorvastatin contributes to inhibition of the progression of atherosclerosis [14]. Renal transplantation is often coupled with several complications, such as dyslipidemia, as well as mineral and bone disorders [15-20,35]. Statins reduce the incidence of cardiovascular events and decrease the morbidity and mortality of renal patients whether on dialysis or following transplantation [13,25,27,30]. Furthermore, elderly patients are increasingly being considered for renal transplantation [24,36]; these patients often have several co-morbidities. Thus, statin use in this category of patients is virtually mandatory to reduce post-transplant dyslipidemia, as well as morbidity and mortality rates. Finally, future trials should also verify the predictability of several markers of acute/chronic allograft failure, such as serum levels of soluble CD [30,37].

## CONCLUSION

We suggest that oxidative modification of HDL can affect their ability to reduce antioxidant and PON-1 activity, but statins treatment improves them and can prevent progression of atherosclerosis and chronic allograft failure. However, future studies are required.

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## SUMMARY

Disturbances in the metabolism of the lipoproteins in post-renal transplant patients accelerate atherosclerosis and cardiovascular diseases, which are one of the major causes of death from these diseases. Serum concentration of lipid, lipoprotein, leptin, total peroxide (OxyStat), and

paraoxonase-1 activity (PON1) were determined in 11 post-renal transplant patients (Tx) with stable renal function and normolipidemia, 25 Tx patients without statins therapy, 31 Tx patients with statins therapy and 53 controls. Tx patients received prednisone and Cyclosporine A or prednisone and prograf. Tx patients with stable renal function and normolipidemia had favourable clinical and laboratory parameters and lipid and lipoprotein profiles than those without statins and with statins therapy. Tx patients with dyslipidemia had disturbed lipoprotein concentration and composition, and triglyceride-rich lipoproteins (TRLs) and HDL metabolism. VLDL, IDL, LDL and HDL particles were smaller, denser and more susceptible to modification and oxidation. They were exposed to oxidative stress, and the anti-oxidative role of PON-1 was weakened. However, Tx patients with statins therapy had a lower OxyStat level and higher PON-1 basal and salt stimulation activity than Tx patients without statins therapy. We suggest that oxidative modification of HDL can affect their ability to reduce antioxidant and PON-1 activity, but statin treatment improves them, which could prevent progression of atherosclerosis and chronic allograft failure. However, future studies are required.

*Keyword*: lipids, lipoproteins, paraoxonase-1 activity, oxidative stress, post-renal transplant

## STRESZCZENIE

Zaburzenia metabolizmu lipoprotein pacjentów po transplantacji nerki (Tx) przyspieszają miażdżycę i choroby sercowo-naczyniowe, które są główną przyczyną śmierci tych chorych. Stężenie lipidów, lipoprotein, leptyny, całkowitych utleniaczy (OxyStat) i aktywność paraoksonazy1 (PON-1) były oznaczane w surowicy 11 pacjentów Tx ze stabilną funkcją nerki i z normolipidemią, 25 pacjentów Tx bez i 31 po leczeniu statynami oraz 53 pacjentów kontrolnych. Pacjenci Tx otrzymywali prednizon, Cyclosporynę A oraz prednizon i prograf. Pacjenci ze stabilną funkcją nerki i z normolipidemią mieli korzystne kliniczne i laboratoryjne parametry oraz lipidowy i lipoproteinowy profil w porównaniu do pacjentów bez i po leczeniu statynami. Tx pacjenci z dyslipidemią mieli zaburzone stężenie i skład lipoprotein oraz metabolizm lipoprotein bogatych w triglicerydy (TRLs) i HDL. VLDL, IDL, LDL, HDL cząstki były mniejsze, gęstsze i bardziej narażone na stres oksydacyjny, a anty-oksydacyjna ochrona (aktywność PON-1) była osłabiona. Jednakże pacjenci Tx leczeni statynami mieli niższe stężenie OxyStat i wyższą aktywność PON-1 podstawową i aktywowaną NaCl niż pacjenci Tx nieleczeni statynami. Wnioskujemy, że oksydacyjna modyfikacja HDL może oddziaływać na ich zdolność do redukcji anty-oksydacyjnej aktywności PON-1 ale leczenie statynami poprawia je, co może hamować progresję miażdżycy i przewlekłe odrzucanie przeszczepu. Jednakże wymagane są dalsze badania.

*Słowa kluczowe*: lipidy, lipoproteiny, stres oksydacyjny, paraoksonaza1, transplantacja nerki