Available online at www.sciencedirect.com
ScienceDirect
Metabolism Clinical and Experimental 56 (2007) 1714 – 1718
Metabolism
Clinical and Experimental
www.elsevier.com/locate/metabol

Decreased peroxisome proliferator–activated receptor α gene expression is associated with dyslipidemia in a rat model of chronic renal failure

Yusaku Mori, Tsutomu Hirano*, Masaharu Nagashima, Yuji Shiraishi, Tomoyasu Fukui, Mitsuru Adachi

First Department of Internal Medicine, Showa University, School of Medicine, Shinagawa-ku, Tokyo 142-8666, Japan

Received 2 April 2007; accepted 25 July 2007

Abstract

The transcription factor peroxisome proliferator–activated receptor (PPAR) α plays an important role in lipid homeostasis. In this study, we examined whether the down-regulation of PPAR-α gene expression is associated with dyslipidemia in a rat model of chronic renal failure (CRF). Rats with laboratory-induced uremia by 5/6 nephrectomy were bled at 2 weeks and 10 weeks after the nephrectomy to produce conditions. For the sake of convenience, the rats observed at postoperative week 2 were defined as *acute renal failure* (*ARF*) and those observed at week 10 were defined as *CRF*. Lipids in lipoprotein fractions were measured by high-performance liquid chromatography. The abundance of PPAR-α messenger RNA (mRNA) in the liver was measured by reverse transcriptase–polymerase chain reaction. Serum creatinine and blood urea nitrogen levels rose with the progression of renal failure, but the total protein levels remained constant. Serum triglyceride in ARF rats remained unchanged from the level in sham-operated control rats, whereas that in CRF rats was 66% higher than the control level. Serum cholesterol was elevated 1.5-fold in ARF rats and 2-fold in CRF rats compared with the sham-operated counterparts. As with triglyceride, very low-density lipoprotein remained unchanged in ARF rats but rose substantially in CRF rats. All of the major lipoprotein fractions were elevated in CRF rats. These lipid and lipoprotein changes were significantly associated with creatinine and blood urea nitrogen levels. The PPAR-α mRNA expression in the liver was unchanged in ARF rats but was 44% lower in CRF rats. The PPAR-α mRNA expression was inversely correlated with serum creatinine and lipids in the overall rats. Our results indicate that PPAR-α mRNA expression is down-regulated in the liver of CRF rats and that this down-regulation may play a crucial role in the development of dyslipidemia.

1. Introduction

The high incidence of coronary heart disease (CHD) in patients with chronic renal failure (CRF) results in high morbidity and mortality [1-3]. The pathogenesis of CHD in CRF is multifactorial, whereas dyslipidemia is thought to be a strong risk factor for CHD and other atherosclerotic diseases [4,5]. A number of earlier studies revealed that the lipoprotein profiles of CRF patients are frequently atherogenic, with low levels of high-density lipoprotein cholesterol (HDL-C) accompanying elevated levels of very low-density lipoprotein (VLDL) and intermediate-density lipoprotein [6,7]. Although much remains to be learned of the lipoprotein metabolism in CRF, kinetic studies have revealed a severe impairment of triglyceride-rich lipoprotein (TGRL) catabolism [8-10]. Patients with CRF exhibit reduced levels of lipoprotein lipase (LPL) [11], a rate-limiting enzyme for TG hydrolysis, together with elevated levels of apolipoprotein (apo) C-III, a functional protein known to inhibit VLDL catabolism [12,13]. The low LPL and high apo C-III in CRF may partly explain the mechanisms of defective VLDL catabolism in CRF patients, but the pathogenesis behind these changes has yet to be clarified.

The transcription factor peroxisome proliferator–activated receptor (PPAR) α plays an important role in lipid homeostasis [14]; and fibrate, an agonist for PPAR-α, ameliorates hypertriglyceridemia and low HDL-C [15]. The activation of PPAR-α decreases TG production by enhancing fatty acid oxidation in the liver and facilitates TG removal by stimulating LPL production and suppressing apo C-III production. Peroxisome proliferator–activated receptor α also increases the levels of HDL-C by stimulating the production of apo A-I and A-II [14,15]. We speculated that PPAR-α gene expression

* Corresponding author. Tel.: +81 3 3784 8532; fax: +81 3 3784 8742.
E-mail address: hirano@med.showa-u.ac.jp (T. Hirano).

0026-0495/$ – see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2007.07.016

may be down-regulated in CRF and that this down-regulation could play a crucial role in the development of dyslipidemia. In the present study, we use 5/6 nephrectomized rats, a standard animal model for CRF, to investigate the mechanisms behind the alterations of PPAR-α gene expression in CRF and to identify the associations between PPAR-α gene expression and changes in lipoprotein profiles.

2. Materials and methods

2.1. Induction of uremia and experimental protocol

Male Wistar rats (Sankyo Labo Service, Tokyo, Japan) weighing approximately 200 g at the start of the investigation were kept in individual cages on a rotating 12-hour light-dark cycle with free access to tap water and food containing 60% vegetable starch, 5% fat, and 24% protein (Oriental Yeast, Tokyo, Japan). Uremia was induced using the method reported by Kaufman et al [16], with modification. The rats were anesthetized with an intraperitoneal injection of sodium pentobarbital (Dainippon Sumitomo Pharma, Osaka, Japan; 30 mg/kg of body weight) and randomly assigned to experimental and control groups. The experimental animals underwent complete right nephrectomies, and the control rats underwent sham operations with detachment of intact adrenal gland from the kidney. Seven days later, the experimental animals underwent 2/3 nephrectomies of the hypertrophied left kidneys; and the control rats underwent sham operations as before. Each group was then divided into 2 subgroups for separate observations at 2 and 10 weeks after the second operation to assess alterations in the serum lipid profiles in association with the duration of CRF. For the sake of convenience, the rats observed at postoperative week 2 were defined as *acute renal failure* (*ARF*) and those observed at week 10 were defined as *CRF*. The experimental procedures at the end of each observation period were conducted from 8:00 to 10:00 AM after a 16-hour fast (food was removed at 4:00 PM on the previous day; drinking water remained available). Blood samples were collected from the jugular vein under sodium pentobarbital (Dainippon Sumitomo Pharma, 55 mg/kg of body weight) anesthesia. A volume of 15% (wt/vol) EDTA (final EDTA concentration, 0.15%) was added to the blood, and whole plasma samples were isolated (800*g*, 20 minutes, 10°C). Aliquots were frozen (−20°C) for future lipid analyses and for measurement of plasma urea nitrogen and creatinine. Small pieces of liver (approximately 0.2 g) were collected and rapidly frozen in liquid nitrogen. The tissues were stored at −80°C until analysis.

All animal procedures were conducted in accordance with the *Guide for the Care and Use of Laboratory Animals* of Showa University and approved by the Committee for the Care and Use of Animals of the same institution.

2.2. Gene expression of PPAR-α in liver

The levels of PPAR-α and β-actin gene expression in the livers of nephrectomized and sham-operated rats were measured by reverse transcriptase–polymerase chain reaction (RT-PCR). Total RNA was extracted from frozen liver using ISOGEN reagent (Nippon Gene Co, Tokyo, Japan). The RNA concentrations of the extracts were determined from the absorbance at 260 nm, and all samples had a 260/280 nm absorbance ratio of about 2.0. Reverse transcription to complementary DNAs was carried out with 1000 ng of total RNA using a ReverTra Dash RT-PCR kit (Toyobo, Osaka, Japan) with a mixture of 10 mmol/L dNTP Mixture, 10 U/μL and 10 pmol/μL RNase Inhibitor and Primer (sequence 5′-$(dt)_{20}$-3′) in a 20-μL volume for 10 minutes at 30°C and 20 minutes at 42°C. The reaction was halted by heating at 99°C for 5 minutes. The complementary DNA was amplified using a ReverTra Dash RT-PCR kit (Toyobo) with 10× PCR buffer, a 10-pmol/μL PPAR-α primer set, a 10-pmol/μL β-actin primer set, and 2.5 U/μL KOD Dash (Toyobo) in 25 μL of total volume. The PCR was carried out in 35 cycles (98°C for 10 seconds, 60°C for 2 seconds, 74°C for 30 seconds, and a final elongation step of 1 minute at 74°C) for PPAR-α and β-actin. The following primers were used: PPAR-α forward, 5′-CAA GCT CAG GAC ACA AGA CG-3′; PPAR-α reverse, 5′-CTC AGC CAT GCA CAA GGT CT-3′ (GenBank accession number NM013196); β-actin forward, 5′-ACT GGC ATT GTG ATG GAC TC-3′; β-actin reverse, 5′-GTG GTG GTG AAG CTG TAG CC-3′ (GenBank accession number NW031144). The PCR products were separated on a 1% agarose gel by electrophoresis. Band intensities were compared by imaging ethidium bromide staining and quantified using image processing and analysis in Java. The values were normalized for the corresponding amount of β-actin messenger RNA (mRNA).

2.3. Biochemical assays

Plasma levels of total cholesterol (TC), TG, nonesterified fatty acid (NEFA), HDL-C, blood urea nitrogen (BUN), and creatinine were measured in duplicate spectrophotometrically with standard commercial kits (Wako Pure Chemical Industries, Osaka, Japan). Quantifications of cholesterol and TGs in lipoproteins and plasma lipoproteins were classified on the basis of differences in particle sizes in the cholesterol and TG profiles of lipoproteins quantified by high-performance liquid chromatography according to the method used by Hara and Okazaki [17] in their analyses of serum lipoprotein fractions in rodents [18].

Significant differences were determined by Mann-Whitney *U* test. Correlation coefficients between 2 variables were calculated by Pearson simple linear regression analysis. Statistical significance was accepted at $P < .05$.

3. Results

3.1. General profiles and serum lipids in sham-operated and 5/6 nephrectomized rats

The nephrectomies led to decreases in food intake and body weight (Table 1). As expected, BUN and creatinine were significantly elevated in the ARF rats and even further

Table 1
General profiles and serum lipids, containing TG and cholesterol in the major lipoprotein fractions, of sham-operated and 5/6 nephrectomized rats

	ARF model		CRF model	
	Sham operation	5/6 Nephrectomy	Sham operation	5/6 Nephrectomy
n	6	6	6	6
Age (wk)	8	8	16	16
Post operation (wk)	2	2	10	10
Body weight (g)	242 ± 5	207 ± 5 *	313 ± 8	295 ± 23
Food intake (g/d)	25	23	NA	NA
TC (mg/dL)	50 ± 6	71 ± 7 *	63 ± 7	153 ± 69 †, ‡
TG (mg/dL)	36 ± 13	23 ± 4	42 ± 12	101 ± 31 †, ‡
HDL-C (mg/dL)	42 ± 7	56 ± 6 §	52 ± 5	107 ± 42 †, ‡
Non–HDL-C (mg/dL)	8 ± 4	14 ± 1	12 ± 1	46 ± 28 †, ‡
BUN (mg/dL)	13.5 ± 1.3	29.9 ± 1.9 *	23.5 ± 3.6	38.4 ± 5.6 †, ‡
Serum creatinine (mg/dL)	0.19 ± 0.09	0.45 ± 0.07 *	0.41 ± 0.14	0.90 ± 0.37 †, ‡
NEFA (mmol/L)	0.41 ± 0.10	0.57 ± 0.18	0.71 ± 0.26	0.74 ± 0.18
Total protein (g/dL)	5.0 ± 0.1	5.3 ± 0.2	5.6 ± 0.9	5.5 ± 0.4
VLDL-TG	23.6 ± 10.5	14.1 ± 3.8	29.0 ± 10.5	74.7 ± 25.3 †, ‡
LDL-TG	8.6 ± 1.9	7.2 ± 1.0	9.8 ± 1.2	20.7 ± 4.7 †, ‡
HDL-TG	2.5 ± 0.7	1.6 ± 0.2	2.5 ± 0.8	4.0 ± 1.3 ‖, ‡
VLDL-C	2.4 ± 0.5	2.8 ± 1.6	2.7 ± 0.5	10.9 ± 7.0 †, ¶
LDL-C	7.0 ± 0.9	12.1 ± 1.6 *	9.4 ± 1.1	35.3 ± 20.5 †, ‡
HDL-C	42.1 ± 7.1	56.4 ± 6.1 §	51.7 ± 5.3	107.0 ± 41.6 †, ‡

Values are means ± SD. NA indicates not available.
* $P < .01$ vs 2 weeks sham.
† $P < .01$ vs 10 weeks sham.
‡ $P < .01$ vs 2 weeks nephrectomy.
§ $P < .05$ vs 2 weeks sham.
‖ $P < .05$ vs 10 weeks sham.
¶ $P < .05$ vs 2 weeks nephrectomy.

elevated in the CRF rats. On the other hand, there were no significant alterations in the serum total protein levels in the acute and chronic uremic animals compared with their respective controls. The NEFA levels were no higher in the uremic rats than in the control rats, but the levels in older rats tended to exceed those in younger rats irrespective of the presence of uremia. The TG levels were no higher in the ARF rats than in the controls, whereas the levels of TC, HDL-C, and, non–HDL-C in the ARF animals exceeded the controls by 34% to approximately 48%. In contrast, the CRF rats exhibited 66% and 100% elevations in serum TG vs the levels measured in sham-operated counterparts and in ARF rats, respectively. Total cholesterol, HDL-C, and non–HDL-C all markedly increased with the progression of renal failure; and the levels measured in the CRF rats were all about double those measured in the ARF rats. The VLDL-TG and low-density lipoprotein (LDL)–TG were both substantially elevated in CRF rats but were more or less unchanged in ARF rats. The HDL-TG levels were lower in ARF rats but were significantly higher in CRF rats, compared with the respective controls. The VLDL-C was substantially elevated in CRF rats but was more or less unchanged in ARF rats. The LDL-C was significantly elevated in ARF rats and was further elevated in CRF rats. The HDL-C levels were slightly elevated in ARF rats and were further elevated in CRF rats.

Fig. 1 shows the abundance of PPAR-α mRNA in the livers of control and uremic rats. As shown the representative picture, PPAR-α gene expression was comparable between ARF and sham-operated rats, but was substantially weakened in CRF rats. The gene expression data from one sham-operated rat at postoperative week 2 and one sham-operated rat at postoperative week 10 were deleted because background noise interfered with the visibility of the bands. The PPAR-α mRNA-actin ratio was reduced by 44% in CRF rats (n = 6) compared with the ratio in control rats (n = 5).

Fig. 2 shows the relationships of the PPAR-α mRNA-actin ratio with the level of serum TG in the entire study of animals (n = 22). The decreased PPAR-α mRNA-actin ratio

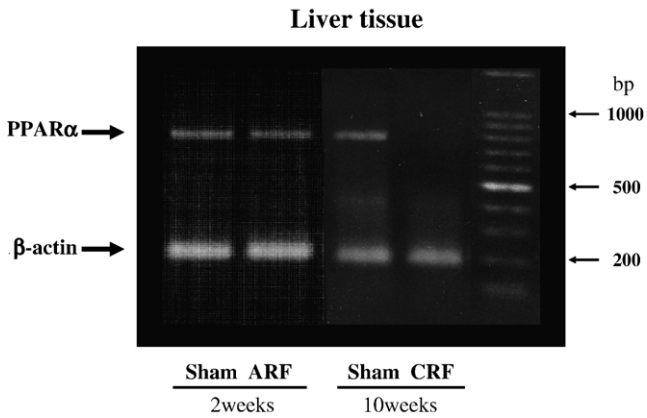

Fig. 1. The PPAR-α gene expression in the liver of ARF and CRF rats with sham operation and 5/6 nephrectomy.

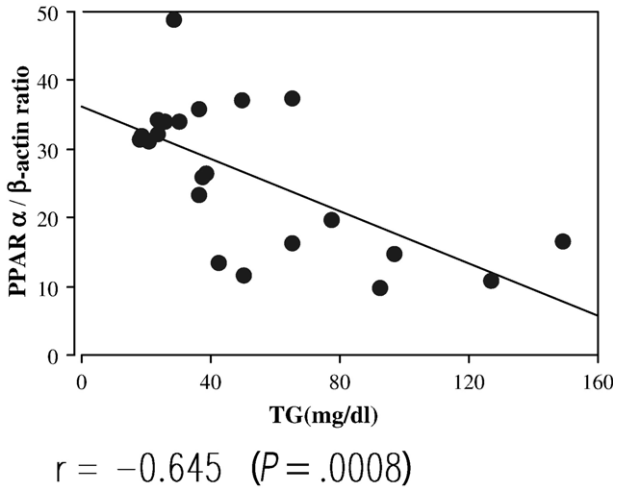

Fig. 2. The relationship between the PPAR-α mRNA-actin ratio and serum TG levels in the entire study of animals (n = 22).

was significantly associated with increased serum TG, decreased non–HDL-C ($r = -0.52$, $P < .02$), increased TC ($r = -0.52$, $P < .02$), decreased HDL-C ($r = -0.51$, $P < .02$), and increases in all of the cholesterol and TG levels in the major lipoprotein fractions ($r = -0.50 \sim 0.72$, $P < .0001 \sim 0.02$). The decreased PPAR-α mRNA-actin ratio did not attain significant correlation with the increase of BUN levels ($r = -0.40$, $P = .063$), but PPAR-α mRNA-actin ratio was significantly associated with the increase of serum creatinine levels ($r = -0.48$, $P = .025$).

4. Discussion

The present study is the first to demonstrate the down-regulation of PPAR-α gene expression in CRF, and this down-regulation was found to be closely associated with CRF-induced dyslipidemia. No decline of PPAR-α gene expression was observed in uremic rats at 2 weeks after the nephrectomy (hereinafter referred to as *ARF rats* for convenience), and the TG levels remained similarly unchanged at that time point in the same animals. Food intake and body weight were significantly reduced in these acute uremic animals; hence, a reduction in the TG level was expected. By week 10 after the nephrectomy (CRF rats), however, the TG levels were markedly elevated and the PPAR-α gene expression was substantially reduced. The decreased PPAR-α gene expression was closely associated with increases of the TG levels in serum and lipoproteins in the total animals, suggesting that low PPAR-α gene expression plays a crucial role in the development of hypertriglyceridemia in CRF. We have corrected the sentences on LPL, as follows: CRF animals generally exhibit decreased plasma activity of heparin-releasable LPL, a rate-limiting enzyme for TG hydrolysis [19,20], and increased concentrations of apo C-III, an inhibitor of the LPL activity and particle uptake induced via lipoprotein receptors [13,20].

The lipid-lowering effects of fibrates (synthetic PPAR-α agonists) have been causally linked to the PPAR-α–dependent stimulation of LPL and an inhibition of apo C-III expressions [15]. It thus stands to reason that a decrease of PPAR-α gene expression will lead to a reduction in LPL activity and an increase in apo C-III production. There have been several TG kinetic studies of 5/6 nephrectomized CRF rats. In studies by Bagdade et al [21] and Roullet et al [22], TG production assessed by the triton WR1339 technique was normal in 5/6 nephrectomized CRF rats, although the animals had low adipose tissue LPL activity. This suggested that the defect in TG catabolism in the CRF animals was mainly attributable to hypertriglyceridemia.

Recent studies have extensively investigated the molecular mechanisms underlying defective TGRL removal in an animal model of CRF. Low-density lipoprotein receptor–related protein [23], VLDL receptors [24], and hepatic triglyceride lipase [25] are all down-regulated in CRF rats; and this down-regulation may bring about the catabolic defect of TGRLs. The mechanisms underlying the catabolic defect in CRF can thus be assumed to be multifactorial, and the decrease of PPAR-α is likely to be one factor.

Cholesterol in serum, LDL, and HDL was elevated by as early as 2 weeks after the nephrectomy, before the down-regulation in PPAR-α expression was observed. It thus appears that PPAR-α was not a requisite for the development of hypercholesterolemia. Later, at 10 weeks after the nephrectomy, the animals exhibited severe hypercholesterolemia concurrently with decreased PPAR-α gene expression. The decrease of PPAR-α gene expression in the total animals was significantly associated with cholesterol in serum or lipoproteins. This tendency remained unchanged when these associations were examined in the subset of CRF rats (data not shown). Thus, we cannot rule out the possibility that the decrease of PPAR-α is involved in the development of not only hypertriglyceridemia, but also hypercholesterolemia, in CRF. A decrease of PPAR-α can be presumed to bring about lower levels of HDL-C because the activation of PPAR-α leads to increases in HDL-C levels by stimulating the structural proteins of HDL, apo A-I, and apo A-II [14,15]. We also found that the CRF rats developed hypertriglyceridemia, a condition usually associated with low HDL-C. Nonetheless, we observed a remarkable elevation of HDL-C levels in the CRF rats. Although the exact mechanisms behind this change are unknown, the lack of cholesteryl ester transfer protein (CETP) in rodents is likely to be involved. The CETP deficiency prevents cholesterol transfer from HDL to apo B–containing lower-density lipoproteins and thereby increases HDL-C even in the presence of down-regulated PPAR-α or hypertriglyceridemia. Hyper–high-density lipoprotein cholesterol, it turns out, has been observed in the presence of low PPAR-α gene expression [26]; and hypertriglyceridemia has been observed in rats with streptozotocin-induced diabetes [27]. We thus should keep the species difference in mind when interpreting the HDL-C level. According to several articles, the liver of CRF rats exhibits a stimulated cholesterogenesis

[28,29] that facilitates the secretion of apo B–containing lipoproteins. Increased activities of the sterol response element binding protein 1 [30] and 3-hydroxy-3-methylglutaryl–coenzyme A reductase [31] play some part in the molecular mechanisms behind the up-regulation of cholesterogenesis. The enhanced cholesterogenesis might bring about hyper–HDL-C in the presence of CETP deficiency.

The impaired removal of apo B–containing lipoproteins resulting from the suppression of LDL receptor–related protein and LDL receptors [20] may also be involved in the molecular mechanisms of hypercholesterolemia in CRF rats. We did not observe low concentrations of serum protein in the nephrectomized rats in the present study. Previous studies have established, however, that 5/6 nephrectomized rats develop mild proteinuria in the chronic phase after their nephrectomies. This may lead to hypercholesterolemia in CRF rats prone to nephrotic syndrome.

The mechanism underlying the suppression of PPAR-α gene expression in CRF rats remains unknown. The PPAR-α expression is up-regulated by glucocorticoids, leptin, growth hormone, and insulin [15]. Paradoxically, however, all of these hormones are usually elevated in CRF. Further studies will be needed to explore how PPAR-α gene expression is down-regulated in CRF and whether the activation of PPAR-α (by fibrate treatment, etc) could attenuate dyslipidemia associated with CRF.

References

[1] Trespalacios FC, Taylor AJ, Agodoa LY, et al. Incident acute coronary syndromes in chronic dialysis patients in the United States. Kidney Int 2002;62:1799-805.

[2] Fried LF, Shlipak MG, Crump C, et al. Renal insufficiency as a predictor of cardiovascular outcomes and mortality in elderly individuals. J Am Coll Cardiol 2003;41:1364-72.

[3] Henry RM, Kostense PJ, Bos G, et al. Mild renal insufficiency is associated with increased cardiovascular mortality: the Hoorn Study. Kidney Int 2002;62:1402-7.

[4] Muntner P, He J, Astor BC, et al. Traditional and nontraditional risk factors predict coronary heart disease in chronic kidney disease: results from the atherosclerosis risk in communities study. J Am Soc Nephrol 2005;16:529-38.

[5] Shoji T, Nishizawa Y. Plasma lipoprotein abnormalities in hemodialysis patients—clinical implications and therapeutic guidelines. Ther Apher Dial 2006;10:305-15.

[6] Wanner C, Quaschning T. Dyslipidemia and renal disease: pathogenesis and clinical consequences. Curr Opin Nephrol Hypertens 2001;10: 195-201.

[7] Shoji T, Ishimura E, Inaba M, et al. Atherogenic lipoproteins in end-stage renal disease. Am J Kidney Dis 2001;38:S30-3.

[8] Prinsen BH, Rabelink TJ, Romijn JA, et al. A broad-based metabolic approach to study VLDL apoB100 metabolism in patients with ESRD and patients treated with peritoneal dialysis. Kidney Int 2004;65: 1064-75.

[9] Ikewaki K, Schaefer JR, Frischmann ME, et al. Delayed in vivo catabolism of intermediate-density lipoprotein and low-density lipoprotein in hemodialysis patients as potential cause of premature atherosclerosis. Arterioscler Thromb Vasc Biol 2005;25:2615-22.

[10] Kaysen GA. Hyperlipidemia of chronic renal failure. Blood Purif 1994; 12:60-7.

[11] Vaziri ND, Liang K. Down-regulation of tissue lipoprotein lipase expression in experimental chronic renal failure. Kidney Int 1996;50: 1928-35.

[12] Moberly JB, Attman PO, Samuelsson O, Johansson AC, Knight-Gibson C, Alaupovic P. Alterations in lipoprotein composition in peritoneal dialysis patients. Perit Dial Int 2002;22:220-8.

[13] Hirano T, Sakaue T, Misaki A, Murayama S, Takahashi T, Okada K, et al. Very low-density lipoprotein apoprotein CI is increased in diabetic nephropathy: comparison with apoprotein CIII. Kidney Int 2003;63:2171-7.

[14] Lefebvre P, Chinetti G, Fruchart JC, et al. Sorting out the roles of PPAR α in energy metabolism and vascular homeostasis. J Clin Invest 2006; 116:571-80.

[15] Staels B, Dallongeville J, Auwerx J, Schoonjans K, Leitersdorf E, Fruchart JC. Mechanism of action of fibrates on lipid and lipoprotein metabolism. Circulation 1998;98:2088-93.

[16] Kaufman JM, Siegel NJ, Hayslett JP. Functional and hemodynamic adaptation to progressive renal ablation. Circ Res 1975;36:286-93.

[17] Hara I, Okazaki M. High-performance liquid chromatography of serum lipoproteins. Methods Enzymol 1986;129:57-78.

[18] Magoori K, Kang MJ, Ito MR, et al. Severe hypercholesterolemia, impaired fat tolerance, and advanced atherosclerosis in mice lacking both low density lipoprotein receptor–related protein 5 and apolipoprotein E. J Biol Chem 2003;278:11331-6.

[19] Vaziri ND, Wang XQ, Liang K. Secondary hyperparathyroidism downregulates lipoprotein lipase expression in chronic renal failure. Am J Physiol 1997;273:F925-30.

[20] Vaziri ND. Dyslipidemia of chronic renal failure: the nature, mechanisms, and potential consequences. Am J Physiol Renal Physiol 2006;290:F262-72.

[21] Bagdade JD, Yee E, Wilson DE, Shafrir. Hyperlipidemia in renal failure: studies of plasma lipoproteins, hepatic triglyceride production, and tissue lipoprotein lipase in a chronically uremic rat model. J Lab Clin Med 1978;91:176-86.

[22] Roullet JB, Lacour B, Yvert JP, Drueke T. Correction by insulin of disturbed TG-rich LP metabolism in rats with chronic renal failure. Am J Physiol 1986;250:373-6.

[23] Kim C, Vaziri ND. Down-regulation of hepatic LDL receptor–related protein (LRP) in chronic renal failure. Kidney Int 2005;67: 1028-32.

[24] Vaziri ND, Liang K. Down-regulation of VLDL receptor expression in chronic experimental renal failure. Kidney Int 1997;51:913-9.

[25] Klin M, Smogorzewski M, Ni Z, et al. Abnormalities in hepatic lipase in chronic renal failure: role of excess parathyroid hormone. J Clin Invest 1996;97:2167-73.

[26] Kanie N, Matsumoto T, Kobayashi T, Kamata K. Relationship between peroxisome proliferator–activated receptors (PPAR alpha and PPAR gamma) and endothelium-dependent relaxation in streptozotocin-induced diabetic rats. Br J Pharmacol 2003;140:23-32.

[27] Bar-On H, Eisenberg S. The metabolic fate of high density lipoprotein (HDL) in the diabetic rat. Diabetologia 1978;14:65-9.

[28] Szolkiewicz M, Sucajtys E, Chmielewski M, et al. Increased rate of cholesterologenesis a possible cause of hypercholesterolemia in experimental chronic renal failure in rats. Horm Metab Res 2002;34: 234-7.

[29] Liang K, Vaziri ND. Upregulation of acyl-CoA: cholesterol acyltransferase in chronic renal failure. Am J Physiol Endocrinol Metab 2002;283:E676-81.

[30] Korczynska J, Stelmanska E, Nogalska A, et al. Upregulation of lipogenic enzymes genes expression in white adipose tissue of rats with chronic renal failure is associated with higher level of sterol regulatory element binding protein–1. Metabolism 2004;53:1060-5.

[31] Chmielewski M, Sucajtys E, Swierczynski J, et al. Contribution of increased HMG-CoA reductase gene expression to hypercholesterolemia in experimental chronic renal failure. Mol Cell Biochem 2003; 246:187-91.