Available online at www.sciencedirect.com
ScienceDirect
Diabetes Research and Clinical Practice 75 (2007) 35–41
DIABETES RESEARCH AND CLINICAL PRACTICE
www.elsevier.com/locate/diabres

Chronic renal failure in diabetic patients increases lipid risk factors for atherosclerosis

Fernando D. Brites *, Karina M. Fernández, Julián Verona, María C. Malusardi, Paula Ischoff, Hugo Beresan, Alicia Elbert, Regina L. Wikinski

Laboratory of Lipids and Lipoproteins, Department of Clinical Biochemistry, School of Pharmacy and Biochemistry, University of Buenos Aires, CONICET, Junín 956 (1113), Buenos Aires, Argentina

Received 28 September 2005; accepted 22 May 2006
Available online 27 June 2006

Abstract

Diabetic patients are at high risk of cardiovascular disease and the risk is amplified in the presence of nephropathy, which may be partially attributed to modifications in lipoproteins. Moreover, lipoprotein profile may be affected by incipient nephropathy, glomerulopathy, and mild or severe renal failure. The aim of our study was to evaluate whether chronic renal failure (CRF) changes lipoprotein profile and apo A-I urinary excretion in diabetic subjects with glomerulopathy in comparison with non-diabetic subjects with glomerulopathy and CRF. Diabetic ($n = 25$) and non-diabetic ($n = 10$) patients with glomerulopathy and CRF showed significantly higher LDL-cholesterol, non-HDL-cholesterol and HDL-triglyceride levels than diabetic individuals without CRF ($n = 10$). Arylesterase and paraoxonase activities did not show any difference between groups. Apo A-I could not be detected in urine samples from diabetic patients without CRF. All diabetic subjects with glomerulopathy and CRF who presented proteinuria above 6.5 g/24 h showed detectable urinary apo A-I (range = 13.1–61.0 mg/24 h). Similarly, all non-diabetic patients with glomerulopathy and CRF who had proteinuria above 8.0 g/24 h also evidenced detectable apo A-I in urine (range = 25.6–557.3 mg/24 h). Urinary apo A-I showed positive and significant correlations with urea ($r = 0.73$, $p < 0.05$) and proteinuria ($r = 0.97$, $p < 0.0001$), and a negative correlation with albumin plasma levels ($r = -0.68$, $p < 0.05$). In conclusion, the presence of CRF in diabetic patients was associated with a more atherogenic lipoprotein profile.

Keywords: Chronic renal failure; Glomerulopathy; Diabetes; Lipoproteins; Atherosclerosis

1. Introduction

The incidence of diabetes is rapidly increasing and already affects a high number of subjects in all the world, with an incidence expected to increase to over two hundred millions by 2010 [1]. Diabetes is a serious and costly disease with micro and macrovascular complications representing the leading causes of morbidity and mortality associated with the condition. Among these complications, diabetic nephropathy affects 40% of type 1 and 10% of type 2 diabetic patients. Moreover, diabetic subjects without or under inadequate treatment may develop renal failure in about 23 years evolution [2].

Patients with diabetes mellitus are at high risk of cardiovascular disease and the risk is further increased when they are complicated with nephropathy [3]. This may be partially attributed to changes in plasma lipids and lipoproteins which may undergo quantitative and qualitative modifications [4,5]. These alterations tend to

* Corresponding author. Tel.: +54 11 4964 8297; fax: +54 11 4508 3645.
E-mail addresses: fbrites@dbc.ffyb.uba.ar, fdbrites@hotmail.com (F.D. Brites).

0168-8227/$ – see front matter
doi:10.1016/j.diabres.2006.05.011

increase the atherogenic potential of some lipoproteins and to decrease the antiatherogenic capacity of others. Moreover, lipid and lipoprotein profile may be affected in different ways by the presence of incipient nephropathy, glomerulopathy, mild or severe renal failure, and sustitutive treatment. Nevertheless, the consequences of these renal affections on lipids and lipoproteins have been scarcely explored in diabetes.

Different studies have evaluated the main features of dyslipidemia in type 1 and type 2 diabetes with or without nephropathy in comparison with healthy individuals [6–8]. Other studies have investigated lipoprotein profile in patients with non-diabetic nephropathy also compared with healthy subjects [9,10].

The aim of our study was to evaluate whether chronic renal failure (CRF) changes lipoprotein profile in diabetic subjects with glomerulopathy in comparison with non-diabetic subjects with glomerulopathy and CRF. The specific aim was to study the changes in lipoprotein concentrations, apolipoprotein (apo) A-I plasma and urinary levels, and the activity of one HDL-associated enzyme named paraoxonase (PON).

2. Materials and methods

2.1. Subjects

We studied 45 Caucasian patients, 10 diabetic subjects with glomerulopathy and without CRF, 25 diabetic individuals with glomerulopathy and CRF, and 10 non-diabetic patients with glomerulopathy and CRF (Table 1). The studied subjects included men ($n = 25$) and women ($n = 20$). Diabetic patients were diagnosed according to the criteria established by the American Diabetes Association [11]. Renal function was considered normal with glomerular filtration rate ranging from 80 to 120 ml/min and CRF was diagnosed when glomerular filtration rate was below 75 ml/min. In non-diabetic patients, glomerulopathy and CRF were confirmed by biopsy, which was not carried out in diabetic subjects due to ethical reasons. Type 1 diabetic patients ($n = 18$) were under treatment with insulin with a dose ranging from 10 to 35 IU daily. Type 2 diabetic patients ($n = 17$) were treated with hypoglycemic drugs and/or insulin. Non-diabetic patients with glomerulopathy and CRF were stable patients. Exclusion criteria were: hepatic, thyroid or acute infectious diseases, pregnancy, and treatment with hypolipidemic drugs, immunosuppressive agents or with glycocorticoids. Ethanol intake was below 15 g/day in all the subjects and individuals who smoked more than 10 cigarettes/day were not included. Patients did not follow a regular exercise training program. Informed consent was obtained from all participants and the protocol was approved by the Ethical Committee from School of Pharmacy and Biochemistry, University of Buenos Aires.

2.2. Study protocol and samples

The day before the test, patients were instructed to follow an isocaloric diet without alcohol intake. After a 12 h overnight fast, venous blood was drawn from the antecubital vein. Samples were taken before the patients received their daily medication. Serum was separated within 30 min by centrifugation at $1500 \times g$, for 15 min, at 4 °C and immediately used for lipoprotein studies. Aliquots were stored at −70 °C. Patients were instructed to collect urine samples during a period of 24 h.

2.3. Analytical procedures

Plasma levels of glucose, fructosamine, urea and creatinine were measured by standardised enzymatic methods (Boehringer Mannheim, Germany) in a Hitachi 717 autoanalyser. HbA_{1c} was evaluated by an inhibition-of-latex agglutination assay (Bayer) (reference range 4.3–5.7%). Albumin levels were determined by immunonephelometry in a Kallestadt autoanalyser. Creatinine and total protein concentrations were measured in urine samples employing standardised enzymatic (Boehringer Mannheim, Germany) and Exton methods [12], respectively. Glomerular filtration rate was then calculated and corrected by standardised body surface.

Table 1
Clinical characteristics from diabetic patients with glomerulopathy and without chronic renal failure (CRF), diabetic patients with glomerulopathy and CRF, and non-diabetic patients with glomerulopathy and CRF (mean ± S.D.)

	Diabetic patients with glomerulopathy and without CRF	Diabetic patients with glomerulopathy and CRF	Non-diabetic patients with glomerulopathy and CRF
N	10	25	10
Age (years)	41 ± 19	49 ± 19	45 ± 16
Sex (M/F)	5/5	15/10	5/5
BMI (kg/m^2)	26.1 ± 5.5	25.6 ± 2.9	27.2 ± 5.6
Waist/hip	0.94 ± 0.09	0.91 ± 0.09	1.01 ± 0.29
Type of diabetes (1/2)	5/5	13/12	–
Duration of diabetes (years)	11 ± 7[a]	19 ± 9	–

BMI, body mass index.
[a] $p < 0.05$ vs. diabetic patients with glomerulopathy and CRF.

Total cholesterol and triglycerides were quantified by standardised enzymatic methods (Boehringer Mannheim, Germany) in a Hitachi 717 autoanalyser. HDL fraction was isolated by precipitation of apo B containing lipoproteins with 20 g/l dextran sulphate (M.W. 50,000) and 1.0 M $MgCl_2$ [13]. Cholesterol and triglycerides were measured in the supernatant by the enzymatic methods previously mentioned, while phospholipids were evaluated following the method of Bartlett [14]. HDL_3 was separated by precipitation of the supernatant containing total HDL with 40 g/l dextran sulphate (M.W. 50,000) and 2.0 M $MgCl_2$ [13]. Cholesterol in HDL_3 fraction was determined by the standardized enzymatic method previously mentioned. HDL_2-C was calculated as the difference between the corresponding values obtained for total HDL and HDL_3. Non-HDL-C was calculated as the difference between total cholesterol and HDL-C. LDL-C level was determined as the difference between total cholesterol and the cholesterol contained in the supernatant obtained after selective precipitation of LDL with 10 g/l polyvinylsulfate in polyetilenglycol (M.W. 600; 2.5%; pH 6.7) [15]. IDL-C levels were quantified following an electrophoretic method previously described [16]. Apo B in serum and apo A-I in serum and urine samples were measured by immunonephelometry in a Kallestadt autoanalyser. For the evaluation of apo A-I levels in urine, samples were previously concentrated 10 folds using sucrose. Evaluation of this procedure showed a sensibility of 0.8 mg/24 h (for 1.0 l of urine per 24 h) and a recovery of 105.8 ± 3.7%. Within-run and between-day variation (CV) for apo A-I determination in urine samples were 1.26 and 3.98%, respectively.

2.4. Paraoxonase/arylesterase activity and phenotype estimation

The enzyme PON 1 was evaluated employing two different substrates: paraoxon (Sigma Chemical Co.; PON activity) and phenylacetate (Sigma Chemical Co.; ARE activity). Both activities were measured in serum samples following the method of Furlong et al. [17].

PON activity was assessed in the presence of 1.0 mol l^{-1} NaCl and results were expressed as nmol ml^{-1} min^{-1}. Measurements were all carried out within the same assay. Within-run precision (CV) for PON activity was 5.5%.

For ARE activity, blanks were included to correct for the spontaneous hydrolysis of phenylacetate. Results were expressed as μmol/ml min and measurements were all carried out within the same assay. Within-run precision (CV) for ARE activity was 4.8%.

PON phenotypic distribution was estimated by the dual substrate method [18]. This consists in plotting PON activity measured in the presence of 1.0 mol l^{-1} NaCl versus ARE activity.

2.5. Data and statistical analysis

Data are presented as the mean ± standard deviation. Differences between groups were tested using unpaired Student's *t*-test or Mann–Whitney *U*-test as appropriate. Correlations between variables were assessed using the Pearson or Spearman test. Differences were considered significant at $p < 0.05$ in the bilateral situation.

3. Results

We studied the effect of the association between diabetes and nephropathy on the lipoprotein profile. The three groups of subjects were not different with respect to age, sex distribution, body mass index, and waist/hip ratio (Table 1). Diabetic patients with glomerulopathy

Table 2
General biochemical parameters from diabetic patients with glomerulopathy and without chronic renal failure (CRF), diabetic patients with glomerulopathy and CRF, and non-diabetic patients with glomerulopathy and CRF (mean ± S.D.)

	Diabetic patients with glomerulopathy and without CRF	Diabetic patients with glomerulopathy and CRF	Non-diabetic patients with glomerulopathy and CRF
Glucose (mg/dl)[a]	229 ± 81[b]	209 ± 105[b]	85 ± 18
HbA_{1c} (%)	9.6 ± 0.9	9.1 ± 2.2	–
Fructosamine (mg/dl)[a]	421 ± 61	418 ± 101	–
Albumin (mg/dl)[a]	3917 ± 522	3559 ± 952	2535 ± 1283
Urea (mg/dl)[a]	37 ± 8[c,d]	75 ± 36	79 ± 47
Creatinine (mg/dl)[a]	0.8 ± 0.2[e,d]	1.8 ± 1.0	1.6 ± 0.9
Glomerular filtration rate (ml/min)	95 ± 14[f,b]	43 ± 18	46 ± 16
Proteinuria (g/24 h)	1.1 ± 0.6[g,d]	4.1 ± 2.9	8.2 ± 6.8

[a] Measured in serum samples.
[b] $p < 0.0005$ vs. non-diabetic patients with glomerulopathy and CRF.
[c] $p < 0.005$ vs. diabetic patients with glomerulopathy and CRF.
[d] $p < 0.05$ vs. non-diabetic patients with glomerulopathy and CRF.
[e] $p < 0.001$ vs. diabetic patients with glomerulopathy and CRF.
[f] $p < 0.0001$ vs. diabetic patients with glomerulopathy and CRF.
[g] $p < 0.05$ vs. diabetic patients with glomerulopathy and CRF.

Table 3
Lipid, lipoprotein, and apolipoprotein profile from diabetic patients with glomerulopathy and without chronic renal failure (CRF), diabetic patients with glomerulopathy and CRF, and non-diabetic patients with glomerulopathy and CRF (mean ± S.D.)

	Diabetic patients with glomerulopathy and without CRF	Diabetic patients with glomerulopathy and CRF	Non-diabetic patients with glomerulopathy and CRF
TG (mg/dl)	147 ± 99	159 ± 88	173 ± 97
TC (mg/dl)	187 ± 39[a,b]	241 ± 72	287 ± 116
HDL-C (mg/dl)	48 ± 17	53 ± 11	63 ± 23
HDL_2-C (mg/dl)	6 ± 5	8 ± 6	13 ± 12
HDL_3-C (mg/dl)	42 ± 13	49 ± 6	50 ± 17
HDL-TG (mg/dl)	14 ± 9[c,d]	19 ± 6	20 ± 6
HDL-PL (mg/dl)	69 ± 22	76 ± 29	101 ± 59
TC/HDL-C	4.2 ± 1.2	4.7 ± 1.5	5.8 ± 1.9
Non-HDL-C (mg/dl)	140 ± 32[c,b]	187 ± 70	235 ± 103
LDL-C (mg/dl)	110 ± 25[c,b]	160 ± 76	199 ± 105
IDL-C (mg/dl)	13 ± 1	15 ± 9	9 ± 6
Apo A-I (mg/dl)	138 ± 30	155 ± 27	154 ± 64
Apo B (mg/dl)	126 ± 41	150 ± 47	154 ± 46

TG, triglycerides; TC, total cholesterol; HDL, high density lipoprotein; PL, phospholipids; LDL, low density lipoprotein; IDL, intermediate density lipoprotein; Apo, apolipoprotein.
[a] $p < 0.005$ vs. diabetic patients with glomerulopathy and CRF.
[b] $p < 0.005$ vs. non-diabetic patients with glomerulopathy and CRF.
[c] $p < 0.05$ vs. diabetic patients with glomerulopathy and CRF.
[d] $p < 0.05$ vs. non-diabetic patients with glomerulopathy and CRF.

and without CRF showed shorter duration of diabetes than subjects with glomerulopathy and CRF.

General biochemical parameters are shown in Table 2. As it was expected, glucose plasma levels were significantly higher in diabetic patients in comparison to non-diabetic subjects, while albumin plasma concentration did not show statistically significant differences. When comparing both diabetic groups, no differences were detected in glucose, HbA_{1c}, or fructosamine levels. Urea and creatinine plasma concentrations, as well as proteinuria, were significantly increased, while glomerular filtration rate was significantly lower in patients with CRF than subjects without CRF.

As regards lipid, lipoprotein and apolipoprotein levels, results are shown in Table 3. Both diabetic and non-diabetic patients with glomerulopathy and CRF showed hypercholesterolemia due to a significant increase in LDL-C levels in comparison to diabetic individuals without CRF. This difference between groups was also evidenced in non-HDL-C concentration. Nevertheless, no statistically significant difference was observed between both groups with CRF. Triglyceride, HDL-C, HDL_2-C, HDL_3-C, HDL-phospholipid, IDL-C, apo A-I and apo B levels were similar in the three groups. HDL-triglycerides were significantly reduced in diabetic patients with glomerulopathy and without CRF than in the other two groups.

Arylesterase and paraoxonase activities, two ways of evaluating an antioxidant enzyme bound to HDL fraction, did not show any difference between the studied

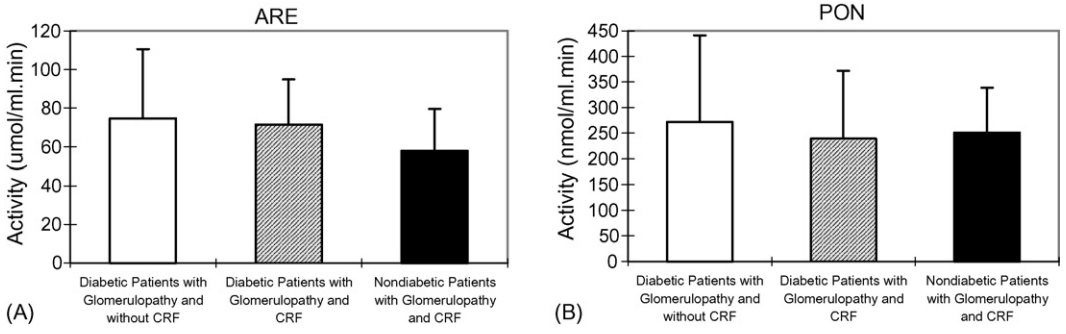

Fig. 1. Arylesterase (ARE) (Panel A) and paraoxonase (PON) (Panel B) activities in diabetic patients with glomerulopathy and without chronic renal failure (CRF), diabetic patients with glomerulopathy and CRF, and non-diabetic patients with glomerulopathy and CRF (mean ± S.D.).

Table 4
Correlation coefficients of urinary apo A-l with different parameters

	Urinary apo A-l	
	r	*p*
Albumin[a]	−0.68	<0.05
Urea[a]	0.73	<0.05
Creatinine[a]	0.09	NS
Glomerular filtration rate	0.24	NS
Proteinuria	0.97	<0.0001

Apo, apolipoprotein; NS, not significant ($p > 0.05$).
[a] Measured in serum samples.

groups (Fig. 1). Paraoxonase phenotypic distribution was also similar in the three groups of patients.

Apo A-I was also evaluated in urine samples from all the participants. This apolipoprotein could not be detected in urine from diabetic patients without CRF. All diabetic subjects with glomerulopathy and CRF who presented proteinuria above 6.5 g/24 h ($n = 6$) showed detectable urinary apo A-I (range = 13.1–61.0 mg/24 h). Similarly, all non-diabetic patients with glomerulopathy and CRF who had proteinuria above 8.0 g/24 h ($n = 5$) also evidenced detectable apo A-I in urine samples (range = 25.6–557.3 mg/24 h). When the correlation coefficients were evaluated between urinary apo A-I and different parameters for the whole group (Table 4), positive and significant correlations were detected for urea and proteinuria, and a negative and significant correlation for albumin plasma levels.

4. Discussion

Diabetes condition did not amplify the lipid risk factors associated with CRF. In this study, CRF patients with or without diabetes exhibited similar lipid and lipoprotein patterns, which were more atherogenic than the profile observed in diabetic patients with glomerulopathy but without CRF. This finding would highlight the fact that CRF represents an important atherogenic risk factor, beyond the presence of diabetes. Accordingly, Alebiosu et al. [19] found a high prevalence of major cardiovascular risk factors among Nigerian subjects with clinical diabetic nephropathy in comparison with type 2 diabetic subjects without nephropathy.

Diabetic patients with glomerulopathy and without CRF showed LDL-C and non-HDL-C levels slightly higher than the recommended values for diabetic subjects [20]. On the other hand, both groups of patients with CRF presented significantly higher total cholesterol, LDL-C and non-HDL-C than diabetic patients without CRF. No statistically significant differences were detected in IDL-C levels among the three groups of patients. In contrast, Kimoto et al. [21] found increased IDL-C concentration in patients with end-stage renal disease which was more pronounced in the presence of diabetes. This adverse effect was accounted for, at least partly, by hypertriglyceridemia associated with chronic hyperglycemia. It must be noted that in our study, triglyceride levels were similar in the three groups. Therefore, the main underlying disturbance in both diabetic and non-diabetic patients with nephropathy from the present study is the accumulation of atherogenic apo B-containing lipoproteins [22].

When we compared both groups with CRF, no differences were detected in the different parameters evaluated. Gonzalez et al. [23] have also shown that lipid and lipoprotein levels were similar in diabetic and non-diabetic patients, both of them with end-stage hemodialysed renal disease. Nevertheless, in those groups of subjects, hemodialysis seemed to improve the lipoprotein profile. Similarly, Joven et al. [24] studied patients with nephrotic syndrome grouped according to the absence or presence of renal failure and/or diabetes mellitus and they found that diabetes mellitus did not affect the pattern of hyperlipoproteinemia of nephrotic syndrome while the characteristic lipoprotein and apoprotein pattern of uremia was present irrespective of nephrosis in uremic, non-diabetic patients. On the other hand, Attman et al. [5] found that diabetic patients with nephropathy presented more pronounced dyslipidemia than non-diabetic subjects with nephropathy. However, those patients had proteinuria levels considerably lower than the subjects evaluated in our study.

Even if plasma levels of HDL-C and HDL-phospholipids showed no statistically significant differences among the studied subjects, a tendency towards higher values may be observed in both groups with CRF. It has been shown that the decrease in plasma colloid osmotic pressure, consequence of the reduction in total protein plasma concentration and hypoalbuminemia, was responsible for the increase in apo A-I and HDL synthesis by the liver and that this synthesis was transcriptionally regulated [25]. This process could be counteracting apo A-I loss via urine in patients with massive proteinuria. Furthermore, Jüngst et al. [26] suggested that the amount of HDL excreted in 24 h urine from patients with nephrotic syndrome was too small to significantly decrease HDL plasma concentration. Moreover, HDL-triglycerides showed a significant increase in both groups with CRF in comparison with diabetic subjects without CRF. In previous studies, we have demonstrated that HDL enrichment in triglycerides reduces its capacity to promote reverse cholesterol

transport, the antiatherogenic pathway by which excess cholesterol is transported from peripheral tissues to the liver for excretion [27]. HDL is also able to protect low density lipoprotein (LDL) against in vitro oxidation [28] and the consequent monocyte-endothelial cell interaction [29]. HDL antioxidant potential can be assigned to different factors such as its chemical composition, the content of liposoluble antioxidants and the presence of associated enzymes like paraoxonase (PON) 1 (EC 3.1.1.2) and platelet-activating factor acethylhydrolase (PAF-AH; EC 3.1.1.47) [30]. In a previous study, we have shown that in type 2 diabetic patients, PON1 activity was similar than in control subjects [31]. In the present work, PON1 activity, evaluated with two different substrates, did not differ among the studied subjects, which would evidence that CRF development did not worsen HDL antioxidant capacity. In contrast, Ikeda et al. [32] showed that PON1 activity was different between type 2 diabetic patients with and without overt proteinuria.

Given that measurement of urinary apo A-I has been shown to reflect the excretion of HDL particles in urine [33], we evaluated this parameter in all the subjects. Only patients with CRF and massive proteinuria eliminated detectable amounts of apo A-I via urine. Accordingly, urinary apo A-I was positively associated with plasma urea and proteinuria, and negatively related to plasma albumin. HDL apolipoproteins may be excreted as small HDL particles or possibly filtered as individual apolipoproteins that recombine to form HDL particles [33]. Horowitz et al. [34] demonstrated that HDL enrichment in triglycerides and further action of lipases increases apo A-I fractional catabolic rate. Accordingly, patients with CRF and detectable urinary apo A-I also had higher HDL-triglycerides. Thus, in these individuals a higher proportion of apo A-I would be present in a more disociable form which may be easily excreted by the kidney.

In conclusion, the presence of CRF in diabetic patients was associated with a more atherogenic lipid and lipoprotein profile consistent of higher total cholesterol, LDL-C, non-HDL-C, and HDL-triglyceride levels, the latter being related with an increase in urinary apo A-I excretion. These results highlight the relevance of preventing CRF development in diabetic patients which clearly increases the risk of atherosclerotic cardiovascular disease.

Acknowledgements

This work was supported in part by Grants from Universidad de Buenos Aires (TB 069), Agencia Nacional de Promoción Científica y Tecnológica (PICT 14299) and CONICET.

References

[1] A.F. Amos, D.J. McCarty, P. Zimmet, The rising global burden of diabetes and its complications: estimates and projections to the year 2010, Diab. Med. 14 (1997) S1–S85.
[2] G. Cornitescu, M. Mota, E. Mota, L. Stanescu, Clinical considerations concerning progressive diabetic renal diseases. Severe complications of early onset diabetes mellitus, Rom. J. Int. Med. 41 (2003) 53–60.
[3] A.J. Jenkins, K.G. Rowley, T.J. Lyons, J.D. Best, M.A. Hill, R.L. Klein, Lipoproteins and diabetic microvascular complications, Curr. Pharm. Dis. 10 (2004) 3395–3418.
[4] T. Hirano, Lipoprotein abnormalities in diabetic nephropathy, Kidney Int. Suppl. 71 (1999) S22–S24.
[5] P.O. Attman, C. Knight-Gibson, M. Tavella, O. Samuelsson, P. Alaupovic, The compositional abnormalities of lipoproteins in diabetic renal failure, Nephrol. Dial. Transplant 13 (1998) 2833–2841.
[6] P. Koskinen, M. Manttari, V. Manninen, J.K. Huttunen, O.P. Heinonen, M.H. Frick, Coronary heart disease incidence in NIDDM patients in the Helsinki Heart Study, Diab. Care 15 (1992) 820–825.
[7] F. Erciyas, F. Taneli, B. Arslan, Y. Uslu, Glycemic control, oxidative stress, and lipid profile in children with type 1 diabetes mellitus, Arch. Med. Res. 35 (2004) 134–140.
[8] M. Laakso, K. Pyorala, H. Sarlund, E. Voutilainen, Lipid and lipoprotein abnormalities associated with coronary heart disease in patients with insulin-dependent diabetes mellitus, Arteriosclerosis 6 (1986) 679–684.
[9] A. Rossi, L. Bonfante, A. Giacomini, A. Calabro, G. Rossi, A. Saller, et al., Carotid artery lesions in patients with nondiabetic chronic renal failure, Am. J. Kidney Dis. 27 (1996) 58–66.
[10] A.B. Haaber, I. Eidemak, T. Jensen, B. Feldt-Rasmussen, S. Strandgaard, Vascular endothelial cell function and cardiovascular risk factors in patients with chronic renal failure, J. Am. Soc. Nephrol. 5 (1995) 1581–1584.
[11] Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, Diab. Care 20 (1997) 183–1197.
[12] K. Gernand, E. Hajek, Comparative study on quantitative cerebrospinal fluid and urinary protein determination with a modified Exton reagent, Dtsch Gesundheitsw 21 (1966) 510–513.
[13] G.R. Warnick, J. Benderson, J.J. Albers, Dextran sulfate-Mg2+ precipitation procedure for quantitation of high-density-lipoprotein cholesterol, Clin. Chem. 28 (1982) 1379–1388.
[14] G.R. Bartlett, Phosphorus assay in column chromatography, J. Biol. Chem. 234 (1959) 466–468.
[15] G. Assmann, H.U. Jabs, U. Kohnert, W. Nolte, H. Schriewer, LDL-cholesterol determination in blood serum following precipitation of LDL with polyvinylsulfate, Clin. Chim. Acta 140 (1984) 77–83.
[16] R.L. Wikinski, L.E. Schreier, S.B. Rosental, New method for isolating and quantifying intermediate and beta-very-low-density lipoprotein cholesterol, Clin. Chem. 37 (1991) 1913–1916.
[17] C.E. Furlong, R.J. Richter, S.L. Seidel, L.G. Costa, A.G. Motulsky, Spectrophotometric assays for the enzymatic hydrolysis of the active metabolites of clorpyrifos and parathion by

plasma paraoxonase/arylesterase, Anal. Biochem. 180 (1989) 242–247.
[18] D.N. Nevin, A. Zambon, C.E. Furlong, R.J. Richter, R. Humbert, J.E. Hokanson, et al., Paraoxonase genotypes, lipoprotein lipase activity, and HDL, Arterioscler. Thromb. Vasc. Biol. 16 (1996) 1243–1249.
[19] C.O. Alebiosu, O. Odusan, O.B. Familoni, A.E. Jaiyesimi, Cardiovascular risk factors in type 2 diabetic Nigerians with clinical diabetic nephropathy, Cardiovasc. J. S. Afr. 15 (2004) 124–128.
[20] Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), JAMA 285 (2001) 2486–2497.
[21] E. Kimoto, T. Shoji, M. Emoto, T. Miki, T. Tabata, Y. Okuno, et al., Effect of diabetes on uremic dyslipidemia, J. Atheroscler. Thromb. 9 (2002) 305–313.
[22] P.O. Attman, O. Samuelsson, P. Alaupovic, Lipoprotein metabolism and renal failure, Am. J. Kidney Dis. 21 (1993) 573–592.
[23] A.I. Gonzalez, L. Schreier, A. Elbert, G. Berg, H. Beresan, G. Lopez, et al., Lipoprotein alterations in hemodialysis: differences between diabetic and nondiabetic patients, Metabolism 52 (2003) 116–121.
[24] J. Joven, C. Villabona, E. Vilella, Pattern of hyperlipoproteinemia in human nephrotic syndrome: influence of renal failure and diabetes mellitus, Nephron 64 (1993) 565–569.
[25] G.A. Kaysen, E. Hoye, H. Jones, A. van Tol, J.A. Joles, Effect of oncotic pressure on apolipoprotein A-I metabolism in the rat, Am. J. Kidney Dis. 26 (1995) 178–186.
[26] D. Jüngst, W.H. Caselmann, P. Kutschera, P. Weisweiler, Relation of hyperlipidemia in serum and loss of high density lipoproteins in urine on the nephrotic syndrome, Clin. Chim. Acta 168 (1987) 159–167.
[27] J.A. Glomset, The plasma lecithin:cholesterol acyltransferase reaction, J. Lipid Res. 9 (1968) 155–167.
[28] M. Macknes, C. Abbot, S. Arrol, P. Durrington, The role of high density lipoprotein and lipid-soluble antioxidant vitamins in inhibiting low density lipoprotein oxidation, Biochem. J. 294 (1993) 829–834.
[29] A.D. Watson, J.A. Berliner, S.Y. Hama, B.N. La Du, K.F. Faull, A.M. Fogelman, et al., Protective effect of high density lipoprotein associated paraoxonase, J. Clin. Invest. 96 (1995) 2882–2891.
[30] M. Navab, S.Y. Hama, G.P. Hough, C.C. Hedrick, R. Sorenson, B.N. La Du, et al., High density associated enzymes: their role in vascular biology, Curr. Opin. Lipidol. 9 (1998) 449–456.
[31] S. Sanguineti, F. Brites, V. Fasulo, J. Verona, A. Elbert, R. Wikinski, et al., HDL oxidability and its protective effect against LDL oxidation in type 2 diabetic patients, Diab. Nutr. Metab. 14 (2001) 21–31.
[32] Y. Ikeda, T. Suehiro, M. Inoue, Y. Nakauchi, T. Morita, K. Arii, et al., Serum paraoxonase activity and its relationship to diabetic complications in patients with non-insulin-dependent diabetes mellitus, Metabolism 47 (1998) 598–602.
[33] Z.A. Gomo, L.O. Henderson, J.E. Myrick, High-density lipoprotein apolipoproteins in urine: I. Characterization in normal subjects and in patients with proteinuria, Clin. Chem. 34 (1988) 1775–1780.
[34] B.S. Horowitz, I.J. Goldberg, J. Merab, T.M. Vanni, R. Ramakrishnan, H.N. Ginsberg, Increased plasma and renal clearance of an exchangeable pool of apolipoprotein A-I in subjects with low levels of high density lipoprotein cholesterol, J. Clin. Invest. 91 (1993) 1743–1752.