DETERMINANTS OF PLASMA OXIDIZED LOW-DENSITY LIPOPROTEINS IN HEMODIALYSIS PATIENTS

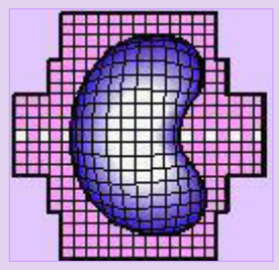
C Căpuşă[1,2], I Stoian[3], C Bărbulescu[4], C Sântimbrean[4], D Dumitru[2], G Mircescu[1,2]

[1] Nephrology Dept., "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

[2] "Dr. Carol Davila" Teaching Hospital of Nephrology, Bucharest, Romania

[3] Biochemistry Dept., "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

[4] "Carol Davila" Fresenius NephroCare Dialysis Center, Bucharest, Romania



BACKGROUND AND AIMS

Peroxidation of low-density lipoproteins (LDL) contributes to the development and progression of atherosclerosis and the roles of circulating oxidized LDL (oxLDL) as both biomarker and pathogenic factor are more and more discussed[1]. Recently, increased concentrations of oxLDL were reported in hemodialysis (HD) patients and assumptions on their involvement to the greater cardiovascular risk in end-stage renal disease patients were made[2].

Although associations of oxLDL levels with lipid profile, metabolic and oxidative stress biomarkers were described in healthy population[3], only scarce data exists for chronic kidney disease patients. Therefore, we aimed to assess the relationships of circulating oxLDL with serum oxidative stress and lipid status parameters in hemodialysis (HD) patients.

SUBJECTS AND METHODS

SUBJECTS:

Fifty-two stable, non-diabetic, non-smoking adults (54% males, 51 [42-57] years) with chronic kidney disease on maintenance HD (77 [31-134] months dialysis vintage, single-used hollow-fiber polysulphone dialyzers, bicarbonate dialysate), without overt inflammation (C-reactive protein <10mg/L) were included in this cross-sectional study.

STATISTICAL ANALYSIS:

Results were expressed as percentages or median with first and third quartiles. Comparisons among subgroups of patients defined by tertiles of oxidized LDL, Spearman rank correlation and multiple linear regression analyses (log-transformed variables) were performed. A *p* value <0.05 was considered significant.

STUDY PARAMETERS:

Oxidized LDL was measured by ELISA (*DRG Diagnostics Germany*).

Serum thiobarbituric acid reactive substances (TBARS), plasma reactive dicarbonyl compounds (RDC), Amadori products (PAmad), plasma total free thiols (PtSH), serum total antioxidant activity (TAA), and arylesterase activity of serum paraoxonase (PON) were assessed by spectrophotometry.
Serum residual antioxidant (RAA) activity was calculated.

Routine biochemistry was used to assess: lipid profile [plasma total cholesterol (tC), triglycerides (TG), HDL-cholesterol (HDL-C), and LDL-cholesterol (LDL-C)], serum albumin and uric acid. Atherogenic index of plasma (AIP, logarithm of molar ratio TG/HDL-C) was calculated as surrogate of lipoprotein particle size[4].

RESULTS

PATIENTS' CHARACTERISTICS ACCORDING TO OXIDIZED LDL

Median oxLDL was 1.7 [1.5-1.8] U/mL.

Subjects in the highest tertile of oxidized LDL had lower plasma total free thiols (p=0.02), *but* higher HD vintage (p=0.01), serum cholesterol (p<0.01), triglycerides (p<0.01), LDL-C (p<0.01), atherogenic index of plasma (p<0.01), and uric acid (p<0.01) as compared to those in the lowest tertile:

Parameter	Tertiles of oxidized LDL		
	T1 (n=18) 1.5 [1.4-1.5]	T2 (n=18) 1.7 [1.6-1.8]	T3 (n=16) 1.9 [1.8-2.0]
Age (years)	47 [42-56]	51 [46-55]	54 [46-60]
Male (%)	50	56	56
Dialysis vintage (months)	64 [22-93]	55 [29-133]	116 [80-159]*
Body mass index (kg/m^2)	22.8 [20.9-26.1]	23.3 [22.3-25.2]	24.7 [22.5-28.7]
Total cholesterol (mg/dL)	171 [161-179]	184 [179-190]	208 [194-223]*
Triglycerides (mg/dL)	88.5 [76-134]	181 [118-223]	174 [144-218]*
LDL-cholesterol (mg/dL)	104 [93-113]	115 [104-123]	132 [116-142]*
HDL-cholesterol (mg/dL)	46.7 [38.4-49.2]	35.4 [33.4-40.8]	42.5 [39.5-44.6]
AIP [log(TG/HDL-C)]	0.29 [0.25-0.44]	0.68 [0.54-0.74]	0.61 [0.53-0.75]*
Serum albumin (g/dL)	4.3 [4.0-4.5]	4.5 [4.1-4.5]	4.4 [4.2-4.6]
Serum uric acid (mg/dL)	5.9 [5.4-6.6]	7.0 [6.4-7.4]	6.7 [6.2-8.0]*
TBARS (nmol/g protein)	15.4 [10.0-21.8]	13.3 [10.1-22.9]	14.5 [12.4-22.9]
RDC (mcmol/g protein)	28.9 [24.9-34.1]	25.9 [24.0-29.5]	29.0 [21.2-36.9]
PAmad (mmol/L)	394 [366-448]	474 [369-502]	467 [417-500]
PtSH (mcmol/g protein)	2.05 [1.82-2.20]	1.98 [1.73-2.32]	1.76 [1.57-1.96]*
TAA (mmol/L)	1.39 [1.27-1.65]	1.57 [1.42-1.69]	1.61 [1.44-1.66]
RAA (mmol/L)	0.68 [0.55-0.84]	0.69 [0.58-0.95]	0.72 [0.51-0.85]
PON (mcmol/min/mL)	31.8 [21.3-52.0]	21.0 [18.6-31.9]	22.3 [16.2-29.3]

* p<0.05 versus the lowest tertile.

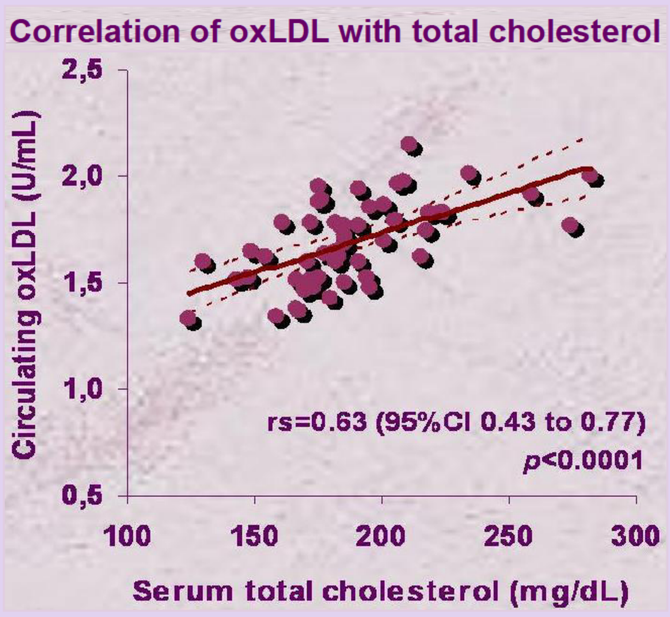
These findings could infer that metabolic abnormalities (hyperlipidaemia and hyperuricaemia) have a preponderant role over oxidative stress for the lipid peroxidation.

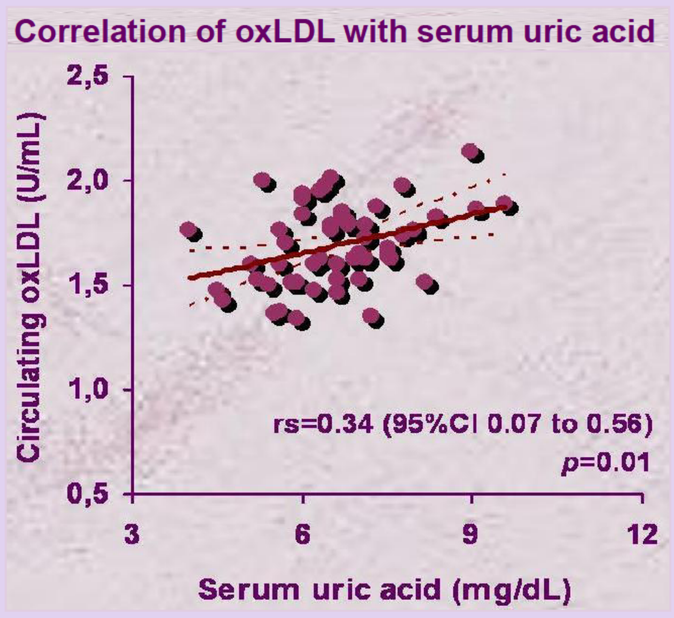
IS OXIDIZED LDL CORRELATED WITH OXIDATIVE STRESS AND LIPID STATUS?

To test the hypothesis suggested by the descriptive analysis, correlation and regression methods were applied.

In the univariate analysis, oxLDL was positively associated with serum total cholesterol, LDL-C, TG and AIP (rs= 0.63, 0.54, 0.53 and 0.47, respectively, p<0.001), dialysis vintage (rs= 0.31, p=0.02), and uric acid (rs= 0.34, p=0.01), while inversely with PON (rs= –0.31, p=0.03) and PtSH (rs= –0.35, p=0.01).

No significant correlations with TBARS and carbonyl compounds were found.





However, multiple linear regression analysis, a model that explains 59% of oxidized LDL variation, retained only total cholesterol (direct), HDL-C (inverse), uric acid (direct), and TAA (inverse) as independent predictors:

Variable	*t* ratio	Std. Beta (95% CI)	*p*
Intercept	-3.9		<0.001
Log(total Cholesterol)	7.1	0,69 (0.35 to 0.63)	<0.001
Log(HDL-Cholesterol)	-3.2	-0,34 (-0.34 to -0.08)	0.002
Log(serum Uric acid)	3.0	0,30 (0.07 to 0.33)	0.004
Log(serum total antioxidant activity)	-2.3	-0,23 (-0.31 to -0.02)	0.03
Adjusted R^2 = 0.56 p<0.001			
Dependent variable: Log(oxLDL)			
Potential predictors entered in step 1: Log(Age), Log(HD vintage), Log(BMI), Log(tC), Log(TG), Log(LDL-C), Log(HDL-C), Log(AIP), Log(serum albumin), Log(serum uric aci), Log(TBARS), Log(PtSH), Log(TAA), Log(RAA), Log(PON), Log(RDC), Log(PAmad)			

CONCLUSIONS

The plasma lipid status, i.e. increased amount of substrate for oxidation along with decreased anti-atherogenic component, appears as essential for a higher level of oxidized LDL in long-vintage HD patients. Also, elevated serum uric acid seems to favor low-density lipoproteins oxidation at least in this clinical setting.

Oxidative stress parameters had weaker influence, only the reduced extracellular antioxidant capacity being an independent contributor of circulating oxLDL.

Therefore, on might speculate on the need to address metabolism abnormalities in the management of hemodialysis patients.

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M) Dialysis. M9) Protein-energy wasting, inflammation and oxidative stress in CKD 5D.

Cristina Capusa

DOI: 10.3252/pso.eu.51era.2014

Poster presented at: 51 ERA-EDTA CONGRESS AMSTERDAM 2014