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The lipoprotein profile in patients with impaired renal function is characterized by an accumulation triglyceride rich particles and shows no evidence of small dense LDL

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Introduction: Fat metabolism disorders are causally involved in the pathogenesis of cardiovascular disease and may be involved in the pathogenesis of renal disease. Chronic kidney disease (CKD) is associated with a dyslipidemia characterized by high levels of triglycerides (TG) and low HDL cholesterol (HDL-C). It is often hypothesized that this also increases the concentration of small dense LDL particles (sdLDL). The aim of our work was to investigate this hypothesis in the Ludwigshafen Risk and Cardiovascular Health (LURIC) study.

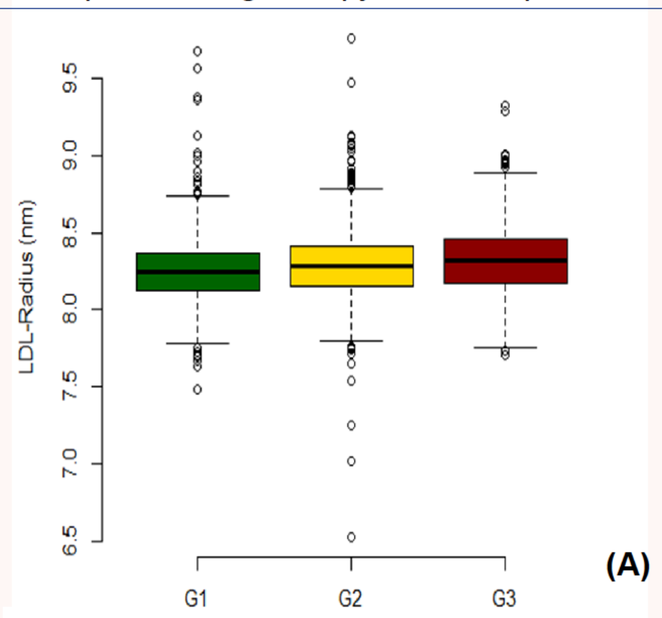
Material and Methods: The LURIC study includes 3316 white patients with indication for coronary angiography. Cholesterol, non-esterified cholesterol, triglycerides, and phospholipids were measured with enzymatic reagents from WAKO (Neuss, Germany) on an Olympus AU640 analyzer. Apolipoproteins were determined by turbidimetry using reagents from Greiner (Flacht, Germany). Lipoproteins were separated by a combined ultracentrifugation-precipitation method (β-quantification). The average radius of LDL was calculated from apoB and major lipids associated with LDL following the method by Baumstark et al.. Serum creatinine was determined using the Jaffé method with CREA test kits (Roche, Mannheim, Germany) on a Hitachi 717 Analyzer. Cystatin C was assayed by immunonephelometry (N-Latex Cystatin C, Dade Behring, Marburg, Germany) eGFR was estimated by using the 2012 CKD-EPI eGFR creat-cys equation. Patients were stratified into three groups according to their eGFR: G1 (eGFR >90 ml/min), G2 (eGFR 60-89 ml/min) and G3 (eGFR < 60 ml/min).

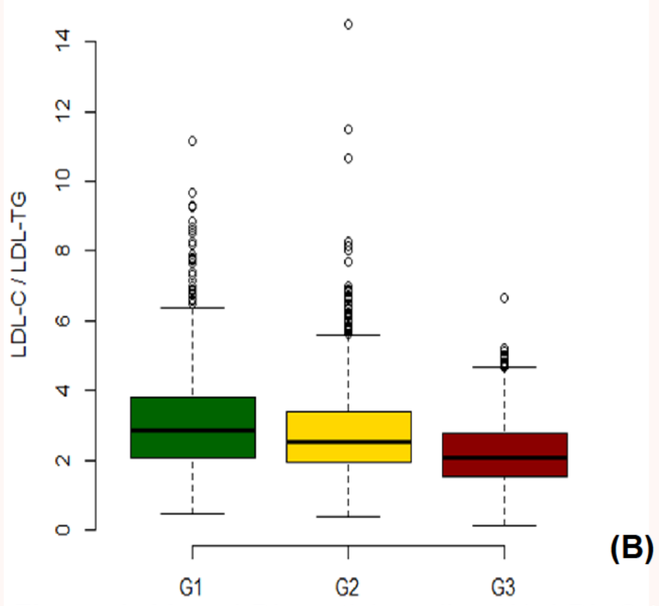
Table 1: Anthropometric data from the LURIC patients stratified by eGFR (Mean ± SD or median and IQR).

	G1: eGFR ≥90 ml/min/1.73m^2 (n=1209)	G2: eGFR 60-89 ml/min/1.73m^2 (n=1642)	G3: eGFR <60 ml/min/1.73m^2 (n=456)	P
Age (years)	55.8±10.2	65.5±8.4	70.8±8.4	<0.001*
Sex (% male)	78.2	66.5	58.1	<0.001**
(Ex-) Smokers (%)	71.2	61.4	57.7	<0.001**
BMI (kg/m^2)	27.2±4.0	27.7±4.0	27.5±4.4	0.020*
Diabetes (%)	30.4	42.4	56.4	<0.001**
CAD (%)	72.9	79.9	83.8	<0.001**
Hypertension (%)	61.9	77.6	84.0	<0.001**
Lipid lowering therapy(%)	48.2	49.3	46.9	0.629**

*) ANOVA; **) Chi- square test

Results: Patients with renal impairment were on average older, more often female and suffered more often from coronary heart disease, diabetes and hypertension (**Table 1**). Regarding the composition of the lipoprotein particles, patients with impaired renal function had lower LDL-C and HDL-C but elevated LDL-TG and HDL-TG (**Table 2**). For both the LDL as well as HDL particles the proportion of TG increased. The ratio of LDL-C to LDL-TG decreased from 4.04 (3.21-5.04) in G1 to 3.14 (2.58-3.99) in G3 (P<0.001; **Figure 1**). The mean radius of the LDL particles was higher in patients with impaired renal function (G1 vs. G3: 8:25±0.21nm vs 8:33±0.24nm; P < 0.001). No significant differences were observed for apolipoproteins B and C2 whereas apoA1 and apoA2 were decreased in group G3 and apoC3 showed a slight increase. Results only for patients without lipid-lowering therapy were comparable.





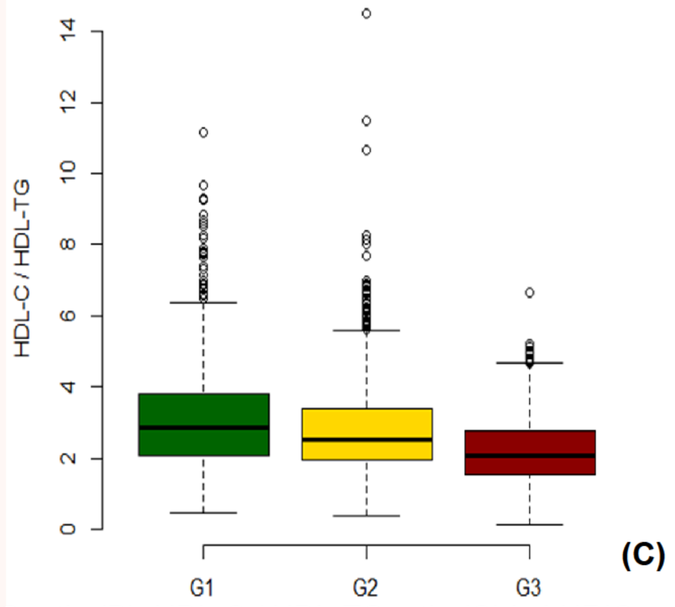


Figure 1: Mean LDL particle radius (A), LDL-C / LDL-TG ratio (B), HDL-C / HDL-TG ratio (C) in LURIC patients with different stages of renal impairment.

Table 2: Plasmalipids in patients stratified by eGFR

	G1 (n=1209)	G2 (n=1642)	G3 (n=456)	P
TC (mg/dl)	194.1 ±40.5	192.6 ±37.4	186.7 ±40.4	0.002*
TG (mg/dl)	144.00 (107.3-200.0)	145.0 (107.0-198.0)	159.00 (118.3-209.0)	0.005**
HDL-C (mg/dl)	39.1 ±10.7	39.0 ±10.8	36.8 ±11.0	<0.001*
HDL-TG (mg/dl)	14.55±6.51	16.15±6.9	18.49±7.68	<0.001*
HDL-C/HDL-TG	2.88 (2.08-3.82)	2.55 (1.93-3.40)	2.09 (1.52-2.78)	<0.001**
LDL-C (mg/dl)	117.3 ±35.2	117.4 ±33.6	111.3 ±34.2	0.002*
LDL-TG (mg/dl)	29.84±10.44	31.61±11.86	35.62±13.70	<0.001*
LDL-C/LDL-TG	4.04 (3.21-5.04)	3.83 (3.06-4.84)	3.14 (2.58-3.99)	<0.001**
ApoA1 (mg/dl)	130.1±25.0	130.3 ±24.7	124.7 ±25.9	<0.001*
ApoA2 (mg/dl)	43.89±9.49	41.01±9.08	37.40±8.92	<0.001*
ApoB (mg/dl)	104.9 ±25.5	104.4 ±23.6	103.2 ±26.0	0.461*
ApoC2 (mg/dl)	4.51±2.61	4.41±2.1	4.36±2.48	0.386*
ApoC3 (mg/dl)	14.44±5.36	14.34±4.73	15.3±5.37	0.001*
LDL particle radius (nm)	8.25±0.21	8.29±0.22	8.33±0.24	<0.001*

*) ANOVA; **)ANOVA after Log-transformation

Discussion and conclusion:

Patients with impaired kidney function showed low HDL-C and higher TG. For both the LDL particles as well as the HDL particles, the proportion of triglycerides was increased as compared to cholesterol. But instead of an increasing percentage of sdLDL we observed an increase in the average LDL particle radius in patients with impaired kidney function. A similar pattern with respect to the change in lipoprotein particle concentration and composition can also be seen in carriers of certain activity-reducing alleles of the hepatic lipase, which is significantly involved in the hydrolysis of triglycerides of remnant particles. We also find a slight increase of apoC3 in patients with renal impairment, which in the liver inhibits both the lipoprotein lipase as well as the hepatic lipase, and thus the absorption of triglyceride rich lipoproteins. In summary, we found evidence of a delayed degradation of remnants of triglyceride rich lipoproteins in patients with renal impairment. This is accompanied by an increase in the average LDL particle radius with no evidence for an accumulation of sdLDL.

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