

APOLIPOPROTEINS: GOOD MARKERS FOR CARDIOVASCULAR RISK IN PATIENTS WITH CHRONIC KIDNEY DISEASE AND DYSLIPIDEMIA

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Abstract

Background and aims. Dyslipidemia (DLP) is a common complication of chronic kidney disease (CKD) and may accelerate its progression. Circulating lipoproteins and their constituent proteins, apolipoproteins, are risk factors for CKD and cardiovascular diseases (CVD). The aim of the study was to determine whether there is a correlation between apolipoproteins and estimated glomerular filtration rate (eGFR) or between apolipoproteins and anthropometrical and laboratory parameters or between evaluated cardiovascular risk (CV) and dyslipidemia/CKD. **Material and methods.** We performed a study on 51 subjects from the Nephrology Department of Emergency Clinical County Hospital of Craiova, from November 2011 to July 2013. **Results.** We found statistically significant correlations between eGFR and Apo A1. Also we found a linear correlation between C-reactive protein (CRP) and Apo B. When we evaluated the CV risk using CRP, we found statistically significant differences between the groups (CKD and DLP, only CKD, only DLP and control group), patients with CKD and DLP showing the highest levels of CRP. **Conclusions.** Elevated levels of Apo A1 are associated with a low rate of CKD. DLP and chronic inflammation play an important role in the progression of CKD. Patients with CKD and DLP had a high cardiovascular risk.

key words: Apolipoproteins, dyslipidemia, chronic kidney disease, inflammation.

Background and aims

Dyslipidemia (DLP) is a common complication of chronic kidney disease (CKD) and may accelerate its progression, but most importantly DLP contributes to the high cardiovascular morbidity and mortality of CKD patients [1-3]. The major determinants of DLP in CKD patients are glomerular filtration rate (GFR), the presence of diabetes mellitus,

severity of proteinuria, use of immunosuppressive agents, modality of renal replacement therapy (RRT) (treatment by hemodialysis, peritoneal dialysis, or transplantation), other comorbidities and the nutritional status [4].

The association between lipid disorders and increased cardiovascular mortality in the general population is a well known fact and patients with

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CKD are at a higher risk of developing cardiovascular diseases (CVD) than the general population [5].

Circulating lipoproteins and their constituent proteins, apolipoproteins, are risk factors for CKD and CVD [6]. Apolipoproteins A1 (Apo A1) and B (Apo B) are the main structural proteins of high-density lipoprotein cholesterol (HDL-C) and, respectively, low-density lipoprotein cholesterol (LDL-C). Levels of Apo B are better than those of LDL-C at reflecting the spectrum of proatherogenic lipid particles (Very-low-density lipoprotein (VLDL), Intermediate-density lipoproteins (IDL) and LDL) [7]. The antiatherogenic role played by Apo A1 appears to be more important than that of HDL-C. Furthermore, the AMORIS (Apolipoprotein-related MOrtality RiSk) [8], INTERHEART [9] as well as other studies showed that the apoB/apo A1 ratio is strongly related to the risk of myocardial infarction, stroke and other cardiovascular events [10-13]. However, many studies showed that elevated levels of Apo A1 are associated with a low rate of CKD [14].

Are apolipoproteins better markers in the assessment of CKD progression in patients with DLP than conventional lipids? Is it possible to use apolipoproteins as targets for lipid-lowering therapy? Starting from these premises the aim of our study was to determine whether there is a correlation between apolipoproteins and eGFR or between apolipoproteins and anthropometrical measurements, laboratory parameters and evaluated cardiovascular risk (CV).

Material and methods

The study group included 51 subjects, 13 subjects with CKD and DLP, 13 subjects only with CKD, 13 subjects only with DLP, recruited from the Nephrology Department of Emergency Clinical County Hospital of Craiova and 12

control subjects, from November 2011 to July 2013. Was considered to have dyslipidemia patients with lipid-lowering therapy, those who had a diagnosis of dyslipidemia in previous medical records or those who had higher than normal lipid values considered by the National Cholesterol Education Program Adult Treatment Panel III Guidelines (2004 Update) [15] and American Association of Clinical Endocrinologists' Guidelines for Management of Dyslipidemia and Prevention of Atherosclerosis (2012) [16]. CKD was classified based on Cause, GFR category (G1-G5), and Albuminuria category (A1-A3), according to the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 [17]. For the 26 subjects with CKD, the diagnostic criteria were: in 20 subjects CKD was defined as decreased GFR and for 6 subjects CKD was defined by one or more markers of kidney damage (albuminuria ≥ 30 mg/24 hours; ≥ 30 mg/g [≥ 3 mg/mmol], urine sediment abnormalities, electrolyte and other abnormalities due to tubular disorders, abnormalities detected by histology, structural abnormalities detected by imaging, history of kidney transplantation). eGFR was calculated according to the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation [18]. All patients signed an informed consent prior to inclusion in the study.

For all the subjects included in the study, the following inclusion criteria were met: no recent history of acute diseases, no history of oncological diseases and a normal liver function. For each subject we collected the demographic data, laboratory data such as: serum levels of creatinine, total cholesterol (TC), TG, HDL-C, LDL-C, blood glucose, C-reactive protein (CRP), apo A1 and apo B, current therapy and medical history. The CV risk was estimated using total CRP. For CV risk assessment the American Heart Association/Centers for Disease

Control and Prevention (AHA/CDC) guidelines recommend using high-sensitive CRP (hsCRP), (CRP<1mg/l low, CRP 1-3 mg/l average and CRP>3 mg/l high cardiovascular risk) [19]. Routine laboratory data except urea and serum creatinine (conducted in Emergency Clinical County Hospital of Craiova Laboratory) were performed at the Synevo Laboratory in Craiova.

Statistical Analysis

The data were analyzed by the Biostatistics Department of the University of Medicine and Pharmacy of Craiova, Romania, using Microsoft Excel (Microsoft Corp., Redmond, WA, USA), together with the XLSTAT add-on for MS Excel (Addinsoft SARL, Paris, France) and IBM SPSS Statistics 20.0 (IBM Corporation, Armonk, NY, USA) for data processing. We utilised Spearman test in correlation analysis while for categorical data, in order to evaluate the significance of the association (contingency), we used the Fisher exact test (Chi-square test if appropriate). P-values <0.05 were considered statistically significant.

Results

[Table 1](#) reports the characteristics of the entire study population.

Table 1. Baseline characteristics of the study population.

Total subjects	51
Age (years)	53.39 ± 13.75
Men	47.05% (n=24)
Women	52.94% (n=27)
BMI (Kg/m ²)	21.55±0.77
WC (cm)	79.5±4.94
Blood glucose (mg/dl)	71.5±2.12
Dyslipidemia	
-with DLP	50.98% (n=26)
• With LLT	50% (n=13)
• Without LLT	50% (n=13)
-without DLP	49.02% (n=25)
CKD Stage	
-stage 1-2	60.78% (n=31)
-stage 3-5 predialysis	39.22% (n=20)
Diabetes	
-with T2D	23.52% (n=12)
-without T2D	76.47% (n=39)

Hypertension	
-with hypertension	54.90% (n=28)
-without hypertension	45.10% (n=23)

WC – Waist Circumference; LLT- lipid lowering therapy; T2D- type 2 diabetes

When we analyzed the relationship between eGFR and apolipoproteins we found a statistically significant correlation only between eGFR and Apo A1, a direct linear correlation (Spearman $r = 0.284$, $p = 0.044$), as shown in [Figure 1](#). We did not find statistically significant correlations between eGFR and Apo B or Apo B/Apo A1 ratio.

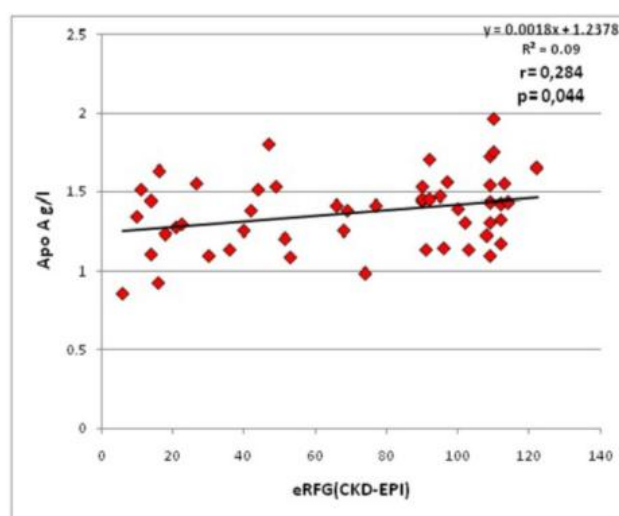


Figure 1. The correlation between eGFR and Apo A1 in the study population.

However, when we analyzed the relationship between Apo B/Apo A1 ratio and the anthropometrical and laboratory parameters we found statistically significant correlations between Apo B/Apo A1 ratio with age (Spearman $r = -0.423$, $p = 0.002$); waist circumference (Spearman $r = -0.343$, $p = 0.014$); body mass index (BMI), (Spearman $r = -0.311$, $p = 0.027$) and blood glucose (Spearman $r = 0.311$, $p = 0.027$), as shown in [Figures 2-5](#).

Taking into consideration that chronic inflammation plays an important role in the pathogenesis and progression of atherosclerosis and CRP is a good marker of inflammation, we have also evaluated the relationship between

CRP and apolipoproteins. We found a linear correlation between CRP and Apo B (Spearman $r = 0.453$, $p = 0.001$) and an inverse linear

correlation between CRP and Apo B/Apo A1 ratio (Spearman $r = -0.410$, $p = 0.003$), as depicted in [Figures 6 and 7](#).

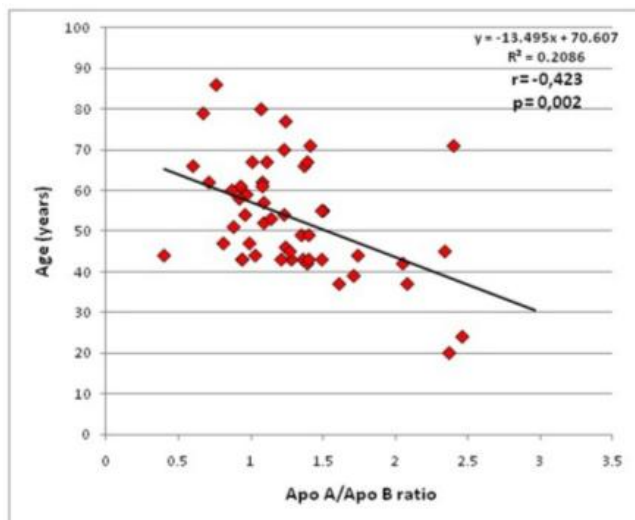


Figure 2. The correlation between Apo B/Apo A1 ratio and age in the study population.

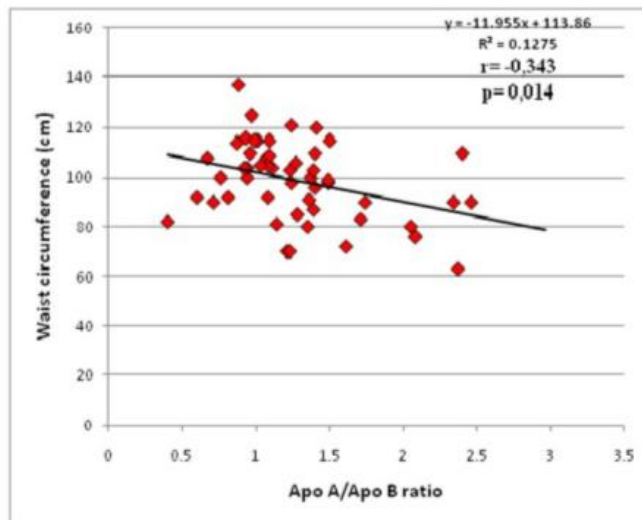


Figure 3. The correlation between Apo B/Apo A1 ratio and waist circumference in the study population.

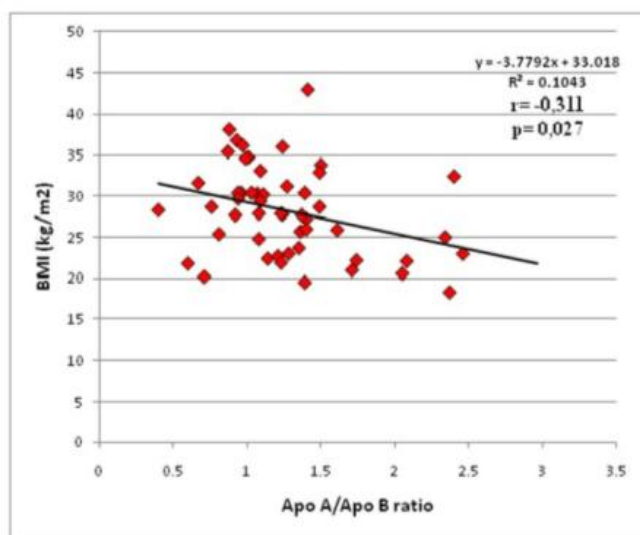


Figure 4. The correlation between Apo B/Apo A1 ratio and BMI in the study population.

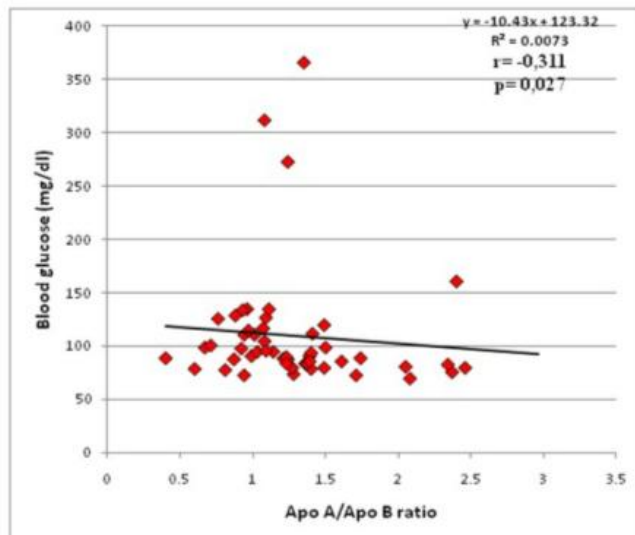


Figure 5. The correlation between Apo B/Apo A1 ratio and blood glucose in the study population.

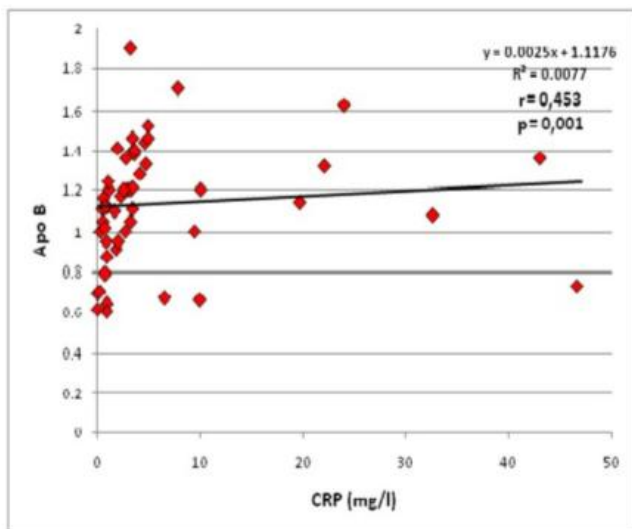


Figure 6. The correlation between CRP and Apo B in the study population.

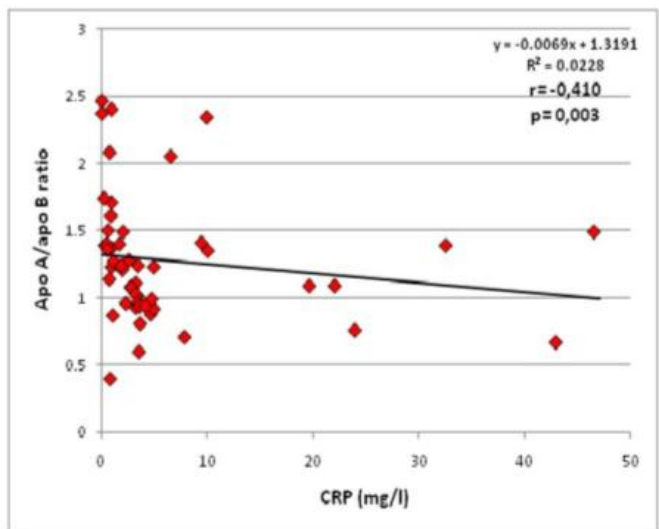


Figure 7. The correlation between CRP and Apo B/Apo A1 ratio in the study population.

Differences between the study groups regarding the cardiovascular risk

Considering that DLP and chronic inflammation play an important role in generating the cardiovascular risk, we have also compared this risk between the groups. We used the Fisher test to analyze the differences between the 4 groups (CKD and DLP, only CKD, only DLP and control group) regarding cardiovascular risk evaluated by CRP levels (CRP<1mg/l, CRP 1-3 mg/l and CRP>3 mg/l) and we found statistically significant differences ($p<0.0001$), as shown in [Figure 8](#).

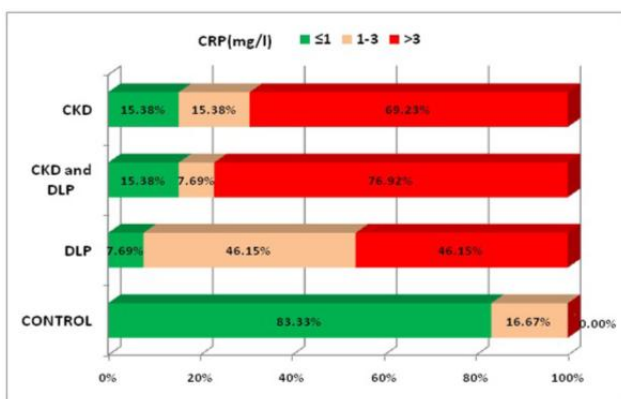


Figure 8. The differences between the groups regarding cardiovascular risk evaluated by CRP levels.

Discussions

The results of our study proved that there is a significant correlation between eGFR and Apo A1, but we did not find a statistically significant correlation between eGFR and Apo B. Our results are concordant with those of two large studies ARIC [20] ($n = 10.292$, 1996-1998) and NHANES III [21] ($n = 7023$, 1988-1991). These studies showed that elevated levels of Apo A1 are associated with a low rate of CKD, but no correlation of eGFR with Apo B could be identified. Regarding the Apo B/Apo A1 ratio both, ARIC and NHANES III studies demonstrated a significant correlation with eGFR but in our study we did not obtained a statistically significant result. However we must also take into consideration a limitation of our study, the small sample size included in the analysis.

DLP and chronic inflammation play an important role in the pathogenesis and progression of atherosclerosis and CKD [22,23]. CRP is a nonspecific indicator of systemic inflammation and also an important marker of atherosclerosis and cardiovascular events [24,25]. In our study, elevated CRP levels were

found in patients with CKD and DLP compared to the other groups. We also found statistically significant correlations between CRP and Apo B and between CRP and Apo B/Apo A1 ratio, confirming data from the literature [26-28].

Regarding the CV risk of the 4 study groups (CKD and DLP, only CKD, only DLP and control group) we found highly statistically significant differences ($p < 0.0001$). However, when interpreting the results of CRP and CV risk, we must take into account that we used for CV risk assessment total CRP and not hsCRP, this representing a major limitation of our study. In addition, some authors suggested that statin therapy may be helpful in lowering CRP levels [29], but we found the highest levels of CRP in the group with CKD and DLP (the only group with lipid lowering therapy).

When interpreting the data presented above, we must also take into consideration the limits of

our study. First, the small sample size of the study group and second, CV was evaluated using total CRP and not hsCRP. These limitations prevent us from drawing strong conclusions.

The results of our study suggest that apolipoproteins levels should not be interpreted singular, but corroborated with those obtained for standard cardiovascular markers (TC, LDL-C, HDL -C, etc.), thereby increasing their predictive value.

Conclusions

Elevated levels of Apo A1 are associated with a low rate of CKD. DLP and chronic inflammation play an important role in the progression of CKD. Patients with CKD and DLP were high cardiovascular risk patients, having also the highest levels of CRP.

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