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Apolipoproteins as predictors of cardiovascular risk in patients with chronic pancreatitis

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Abstract. – OBJECTIVE: Patients with pancreatic diseases are at increased risk of cardiovascular events. Investigating various apolipoprotein forms as important atherogenesis components may improve cardiovascular risk (CVR) prediction. This study aimed to investigate CVR factors in patients with chronic pancreatitis.

PATIENTS AND METHODS: The study enrolled 70 patients (40 males and 30 females, mean age 55.2 years) with chronic pancreatitis and treated pancreatic exocrine insufficiency. We assessed CVR by apolipoproteins A-I, A-II, B, and C-III, lipid profile; score systems [SCORE risk chart and Framingham Risk Score (FRS)], diabetes mellitus; chronic pancreatitis by M-ANNHEIM classification. Statistics were performed *via* SPSS v. 22.

RESULTS: Low apolipoprotein A-I and high apolipoprotein B levels with increased atherogenic potential were observed in 37 and 26 patients. 45.71% demonstrated a high risk of myocardial infarction with high apolipoprotein B/apolipoprotein A-I ratio. Men are at higher CVR risk. Apolipoproteins A-I and A-II correlated with the cardioprotective high-density lipoprotein (HDL) in contrast to apolipoproteins B and C-III, which correlated strongly with low-density lipoprotein (LDL), total cholesterol (TC), and triglycerides (TG). Increased CVR assessed by FRS correlated with significantly lower apolipoprotein A-I and higher apolipoprotein B and apolipoprotein B/apolipoprotein A-I ratio. With the increase in chronic pancreatitis severity, we observed decreased apolipoproteins and increased apolipoprotein B/apolipoprotein A-I ratio.

CONCLUSIONS: Apolipoproteins are valuable CVR indicators. Further studies are required to establish a CVR screening panel in this population.

Key Words:
Chronic pancreatitis, Exocrine insufficiency, Cardiovascular risk, Apolipoprotein, Score system, Lipids.

Introduction

Pancreatic exocrine insufficiency (PEI), regardless of its etiology, is a functional reduction of pancreatic enzyme and bicarbonate secretion, which results in inadequate digestion[1,2]. Maldigestion and malnutrition are typical complications of various primary and secondary pancreatic disorders[3-5]. Fundamental aspects of PEI treatment include pancreatic enzyme replacement therapy (PERT), smoking and alcohol cessation, and intake of small frequent meals without fat restrictions[1,2]. Nowadays, many patients with PEI might be asymptomatic, receiving none or suboptimal PERT. They are at increased risk of PEI complications such as cardiovascular, cachexia, and impaired quality of life, leading to increased mortality[6-9]. According to the World Health Organization[10] data, mortality due to cardiovascular diseases remains the leading cause of death in the European population. American, European, and Canadian guidelines[11-13] recommend a complex approach for a proper cardiovascular risk evaluation, including screening systems, lipid profiles, and apolipoproteins. Atherogenic dyslipidemia is characterized by increased triglyceride and low-density lipoprotein (LDL) levels with decreased high-density lipoprotein (HDL) cholesterol. Low HDL levels are highly associated with the risk of cardiovascular disease development[12,14]. Apolipoproteins serve as cardioprotective or proatherogenic factors. Apolipoproteins have 3 main functions – to modulate lipoproteins enzyme activity, to determine the structural integrity of the lipoprotein complex, and participate in membrane transport of lipoproteins by serving as ligands for specific surface cell receptors[15,16]. Apolipoprotein A is the main apolipoprotein associated with HDL. It has two forms - apolipoprotein A-I and apolipoprotein A-II. Apolipoprotein A-I is a constant protective factor against cardiovascular diseases; however, the impact of apolipoprotein A-II remains unclear[17-21]. Apolipoprotein B provides a direct measurement of all atherogenic circulating lipoprotein particles[17,18,21]. Clinical and epidemiological studies[22-26] confirm

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that apolipoprotein B and apolipoprotein B to apolipoprotein A-I ratio are associated with a worse outcome in patients with cardiovascular diseases. Apolipoprotein B and apolipoprotein B to apolipoprotein A-I ratio are supposed to predict cardiovascular events more accurately than the routinely measured total cholesterol, LDL, total cholesterol/HDL ratio, and non-HDL. Apolipoprotein C-III inhibits the lipolysis of triglyceride-rich lipoproteins and complicates their elimination from the bloodstream. High levels of apolipoprotein C-III are associated with an increased risk of cardiovascular events and atherogenesis[27-29].

Patients and Methods

Study Design and Assessment

Seventy patients diagnosed with chronic pancreatitis were prospectively enrolled in this study. They had PEI (diagnosed by fecal elastase-1) and received PERT (mean dose: 82,000 IU per day). None of the patients has been previously hospitalized due to cardiovascular events (myocardial infarction, stroke, or revascularization procedures). Cardiovascular risk (CVR) was evaluated by apolipoproteins and score systems. Apolipoproteins A-I, A-II, B, and C-III were assessed by immunoturbidimerty (Architect c8000, Abbott, IL, USA), nephelometry (BN ProSpec System, Siemens Healthcare Diagnostics Products GmbH, Germany), spectrophotometry (Architect c8000, Abbott, IL, USA), and ELISA method. According to the European Society of Cardiology[30], levels of apolipoprotein A-I above 120 mg/dL for men and 140 mg/dL for women correspond to normal HDL values. Apolipoprotein B recommended levels do not exceed 120 mg/dL. Based on AMORIS and INTERHEART studies[31,32], the apolipoprotein B to apolipoprotein A-I ratio is used to define the risk of myocardial infarction as low (0.40-0.69 for men and 0.30-0.59 for women), moderate (0.70-0.89 for men and 0.60-0.79 for women) and high (0.90-1.10 for men and 0.80-1.00 for women). Reference ranges for apolipoproteins A-II and C-III is 0.26-0.51 g/L and 6-16 mg/dL, respectively. Using spectrophotometry and immunoturbidimerty (Architect c8000), we further evaluated patients' lipid profiles, including total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL) and triglycerides (TG) in mmol/L. Systematic COronary Risk Evaluation (SCORE Risk Chart) was performed with respect to gender, age, total cholesterol, systolic blood pressure, and smoking status and evaluated the 10-year risk of fatal cardiovascular disease as follows: low risk (score <1%), moderate risk (score ≥1% and <5%), high risk (score ≥5% and <10%) and very high risk (score ≥10%)[30,33]. In addition, we used the Framingham Coronary Heart Disease Risk Score (FRS), which estimates the absolute risk of a heart attack in 10 years, based on gender, age, total cholesterol and HDL, systolic blood pressure, ongoing treatment for hypertension, diabetes mellitus co-morbidity and smoking status. CVR by FRS was defined as low (score <10%), moderate (score between 10 and 19%), and high (score above 20%)[34]. Diabetes mellitus was newly diagnosed based on accepted criteria for fasting glucose levels (above 7.0 mmol/L) and HbA1c levels (above 6.5%). The severity of chronic pancreatitis was assessed by M-ANNHEIM classification[35] and the imaging morphological data by Cambridge classification for CT/MRCP (grade I-IV)[36].

Statistical Analysis

Quantitative data of the statistical analysis were presented as mean, standard deviations (SD), and 95% Confidence Interval for mean, range, or percentages. Quantitative data were analyzed by Student's *t*-test and Mann-Whitney U-test. Measurement data were compared using ANOVA after confirming normal distribution by the Kolmogorov-Smirnov test. Categorical variables were compared, and qualitative data were analyzed by Fisher's exact and linear-by-linear Chi-square tests, as appropriate. Parametric and nonparametric correlations were analyzed by Pearson and Spearman's rho correlations as appropriate. Statistical significance was assumed at a p-value <0.05. Analyzes were performed using the SPSS 22.0 statistical package (IBM Corp., Armonk, NY, USA).

Results

70 patients (40 males and 30 females, mean age 55.2 years) were enrolled in this study. Mean levels of the evaluated apolipoproteins were as follows: apolipoprotein A-I 130.61±29.78 mg/dL, apolipoprotein B 115.00±33.03 mg/dL, apolipoprotein A-II 0.286±0.094 g/L and apolipoprotein C-III 65.46±44.43 g/L. Levels of apolipoprotein A-I below the lower reference limit were ob-

served in 52.86% (n=37, 20 males). High levels of apolipoprotein B were found in 37.14% of all patients (n=26, 16 men). In 11 patients were found both low levels of apolipoprotein A-I and high levels of apolipoprotein B. In this subgroup, 100% had high levels of non-HDL and/or TC/HDL ratio. Apolipoprotein A-II levels were below the reference limit in 18 patients. Apolipoprotein C-III levels were observed above the upper limit in 47 patients. Based on the risk of myocardial infarction, we found low, moderate, and high risk in 20.00%, 30.00%, and 50.00% of males and 13.33%, 46.67 and 40.00% of females, respectively. High risk of myocardial infarction was observed in 45.71% of all patients. Men are at a significantly increased risk of myocardial infarction (p=0.02).

According to the demographic and clinical data, only apolipoprotein A-I depended on gender and was significantly lower in men (122.70±33.80 mg/dL *vs*. 141.12±129.31 mg/dL, p=0.000). With increasing age, only apolipoprotein A-II levels decreased significantly. Apolipoprotein B to A-I ratio was the highest in men (p=0.01). By reporting weight loss in the last 6 months, we observed decreased levels of all investigated apolipoproteins (p<0.05). We found no association of apolipoproteins with reported pain and diarrhea. In addition, body mass index (BMI) correlated moderately with apolipoprotein A-I (r=0.331, p=0.005), A-II (r=0.282, p=0.011), and B (r=0.367, p=0.002). Alcohol consumption (35 patients) and smoking (36 patients) reduced the levels of all apolipoproteins; however, a significant decrease was found only in apolipoprotein C-III levels (49.10±42.08 g/L *vs*. 75.50±45.55 g/L, p=0.009 for alcohol intake and 46.84±33.97 g/L *vs*. 76.29 ±50.34 g/L, p=0.003 for smoking).

We evaluated the relationship between apolipoproteins and lipids (Table I). Apolipoproteins A-I and A-II correlated strongly with HDL. Apolipoprotein B and the ratio of apolipoprotein B to A-I correlated strongly with total cholesterol, LDL, non-HDL, and triglycerides. There was a moderate correlation between apolipoprotein C-III and total cholesterol, LDL, and triglycerides.

We evaluated the correlation between apolipoproteins A-I, A-II, B, and C-III and CVR by score systems. There was no association between CVR by SCORE risk chart and the investigated apolipoproteins (Table II). In contrast, significantly increased CVR based on lower levels of apolipoprotein A-I and higher levels of apolipoprotein A-II was observed with FRS worsening (Table III). Furthermore, the risk of myocardial infarction according to the apolipoprotein B to A-I ratio correlated with significantly higher CVR assessed by FRS (p=0.04) and not with the SCORE risk chart (p>0.05).

We investigated the relationship between the severity of chronic pancreatitis by M-ANNHEIM classification and apolipoproteins (Table IV). Higher levels of apolipoprotein A-I were found in mild chronic pancreatitis compared to moderate (p=0.007) and advanced chronic pancreatitis (p=0.04). Apolipoprotein C-III levels were lower with a severity increase (p=0.047). A similar observation was found between apolipoproteins A-I and C-III and morphological changes worsening in Cambridge classification. Although not sig-

Table I. Correlations between apolipoproteins A-I, A-II, B, and C-III and lipid profile.

	HDL	LDL	TC	TG	Non-HDL
Apolipoprotein A-I	r=0.841 p=0.000	p=NS	r=0.264 p=0.004	p=NS	p=NS
Apolipoprotein B	p=NS	r=0.917 p=0.000	r=0.868 p=0.000	r=0.5799 p=0.000	r=0.941 p=0.000
Apolipoprotein B/A-I ratio	r=-.503 p=0.000	r=0.561 p=0.000	r=0.433 p=0.000	r=0.482 p=0.000	r=0.612 p=0.000
Apolipoprotein C-III	r=0.280 p=0.013	r=0.314 p=0.008	r=0.423 p=0.000	r=0.343 p=0.005	r=0.290 p=0.016
Apolipoprotein A-II	r=0.447 p=0.000	p=NS	r=0.298 p=0.009	p=NS	p=NS

HDL: high-density lipoprotein; LDL: low-density lipoprotein; TC: total cholesterol; TG: triglycerides; NS: not significant.

Table II. Mean levels with a standard deviation of apolipoprotein A-I, A-II, B, and C-III according to CVR by SCORE risk chart.

	High/very high CVR (n=24)	Moderate CVR (n=30)	Low CVR (n=16)	*p*-value
Apolipoprotein A-I (mg/dL)	132.50±36.34	128.85±31.44	131.08±36.59	NS
Apolipoprotein B (mg/dL)	126.95±77.69	114.39±33.61	98.20±77.19	NS
Apolipoprotein A-II (g/L)	0.284±0.073	0.284±0.092	0.289±0.093	NS
Apolipoprotein C-III (g/L)	80.00±45.65	59.00±45.34	57.00±43.15	NS

CVR: cardiovascular risk; NS: not significant.

nificant, a tendency of higher risk of myocardial infarction with chronic pancreatitis progression was observed.

Diabetes mellitus, which is a known factor for high CVR, was diagnosed in 18 patients (25.71%). Although diabetes mellitus has decreased levels of apolipoproteins, this observation did not reach a significant value, $p>0.05$.

Discussion

Impaired nutritional status in PEI patients is further associated with life-threatening cardiovascular complications[8,36]. This prospective study highlights the role of various apolipoproteins as predictors of CVR in patients with PEI due to chronic pancreatitis. In this study, 51.43% of the enrolled patients were smokers, and 25.71% were diagnosed with diabetes mellitus. Most guidelines assess CVR using models to predict the 10-year risk of developing cardiovascular diseases, such as the Framingham Risk Score (FRS) and Systemic Coronary Risk Estimation systems (SCORE). The American Heart Association[34] recommends using FRS, which predicts coronary heart disease through traditional risk factors: age, diabetes mellitus, smoking, systolic blood pressure, ongoing treatment for hypertension, total cholesterol, and HDL cholesterol. Other similar quick systems, including SCORE Risk Chart, use FRS factors or recalibrate Framingham functions to local entities. The European Cardiology Society, in consensus with the European Atherosclerotic Society (ESC/EAS)[30,33,37,38], recommends using the SCORE Risk Chart as it is based on data from a

Table III. Mean levels with a standard deviation of apolipoprotein A-I, A-II, B, and C-III according to CVR by Framingham risk score.

	High CVR (n=19)	Moderate CVR (n=13)	Low CVR (n=38)	*p*-value
Apolipoprotein A-I (mg/dL)	118.97±39.25	130.50±26.80	134.70±30.19	0.007
Apolipoprotein B (mg/dL)	134.47±86.56	118.32±44.92	104.84±25.28	0.02
Apolipoprotein A-II (g/L)	0.262±0.152	0.326±0.088	0.280±0.071	NS
Apolipoprotein C-III (g/L)	75.00±60.50	55.00±36.66	67.00±40.35	NS

CVR: cardiovascular risk; NS: not significant.

Table IV. Mean levels with a standard deviation of apolipoprotein A-I, A-II, B, and C-III according to the severity of chronic pancreatitis by M-ANNHEIM classification.

	Mild CP (n=19)	Moderate CP (n=37)	Advanced CP (n=14)	*p*-value
Apolipoprotein A-I (mg/dL)	146.65±38.39	124.42±31.40	125.22±36.07	0.04
Apolipoprotein B (mg/dL)	119.01±76.74	113.22±32.66	114.16±26.84	NS
Apolipoprotein B/A-I ratio	0.82	0.93	0.96	NS
Apolipoprotein A-II (g/L)	0.32±0.095	0.28±0.095	0.26±0.096	NS
Apolipoprotein C-III (g/L)	94.00±49.55	61.68±45.53	50.18±43.02	0.047

CP: chronic pancreatitis; NS: not significant.

large representative European cohort. These predictive models have become the first-line assessment of CVR in clinical practice. Based on these system scores, patients are classified as having low, moderate, and high CVR. Furthermore, patients are advised to change their lifestyle, which will be investigated by a cardiologist, to start drug therapy or more intensive preventive interventions. By assessing the relationship between the score systems and the studied apolipoproteins, we demonstrated a significant correlation between FRS with apolipoprotein B, apolipoprotein A-I, and apolipoprotein B to apolipoprotein A-I ratio, unlike the SCORE Risk Chart, which did not correlate with any apolipoprotein.

Apolipoprotein A-I is the major HDL-related apolipoprotein that can serve to determine HDL levels in plasma. The main function of apolipoprotein A-I is the removal of excess cholesterol from extra-hepatic tissues. Studies[15,18,30] demonstrate an inverse relationship between HDL-cholesterol and apolipoprotein A-I plasma levels and the risk of coronary disease development in the general population. We also find a strong correlation between apolipoprotein A-I and HDL in patients with chronic pancreatitis. Apolipoprotein A-I levels below the lower reference limit are observed in 52.86% of the studied patients, with significantly lower levels in men. There is no correlation between any other apolipoprotein and gender. In this study, 25.71% of all patients have low levels of apolipoprotein A-II, which correlated strongly with apolipoprotein A-I and apolipoprotein C-III and HDL. Future studies are needed to establish apolipoprotein A-II's role in atherogenesis.

Recent studies[16,39] have demonstrated that apolipoprotein B, which is synthesized in hepatocytes, is a better marker for the concentration of circulating LDL particles and is a more reliable indicator for CVR compared to LDL. LDL is calculated using the Friedewald formula (LDL=TC-HDL-TG/2.2), leading to incorrect results in a number of cases[40]. Apolipoprotein B is part of all atherogenic or potentially atherogenic particles, including LDL, VLDL, IDL, and Lipoprotein (a) [Lp (a)], as each particle contains one molecule of apolipoprotein B. Apolipoprotein B provides a direct measurement of all atherogenic lipoprotein particles in the circulation, which we demonstrate as well by the strong correlations of apolipoprotein B with LDL, TC, non-HDL, and TG. Apolipoprotein B predicts fatal myocardial infarction more accurately than LDL[12,17,18,21,41,42]. Therefore, apolipoprotein B is included in the American Diabetes Association, AHA/ACC, and the Canadian guidelines[11,13]. High levels of apolipoprotein B indicate an increased risk of cardiovascular disease even when total and LDL cholesterol are within the normal range. In our study, high levels of apolipoprotein B were found in 37.14%.

According to case-control, prospective and interventional studies[22-26], apolipoprotein B and apolipoprotein B to apolipoprotein A-I ratio are associated with an unfavorable outcome of cardiovascular diseases and are most probably more specific predictors of CV events than the routinely examined cholesterol, LDL, TC/HDL ratio and non-HDL. The AMORIS and INTERHEART studies[31,32] demonstrate that compared to non-HDL, the apolipoprotein B to apolipoprotein A-I ratio is associated significantly better with the risk of myocardial infarction. The evaluation of apolipoprotein B to apolipoprotein A-I ratio might improve the risk assessment. Using the apolipoprotein B to apolipoprotein A-I ratio, we demonstrated a moderate and high risk of myocardial infarction in 37.14% and 45.71% of all patients, which further correlates with the Framingham Risk Score. The apolipoprotein B to apolipoprotein A-I ratio was significantly higher in men and correlates strongly with LDL, TC, non-HDL, and TG.

Apolipoprotein C-III is an integral part of chylomicrons, VLDL, and HDL. It inhibits the lipolysis of TG-rich lipoproteins and prevents their elimination from circulation[27,28]. In the Monitored Atherosclerosis Regression Study (MARS) and the Cholesterol Lowering Atherosclerosis Study (CLAS), high apolipoprotein C-III levels are strongly associated with the progression of atherosclerotic processes, favoring the development of coronary arterial calcifications, enhancement of monocytic adhesion to vascular endothelial cells and activation of inflammation signal pathways. Low apolipoprotein C-III levels are associated with low triglyceride levels and increased HDL[43,44]. In our study, which is a pilot study that investigates apolipoprotein C-III in patients with pancreatic diseases, we found a moderate correlation between apolipoprotein C-III and atherogenic lipids, as well as a moderate correlation with apolipoprotein A-I, A-II and apolipoprotein B. Alcohol intake and smoking decrease the levels of all apolipoproteins but only apolipoprotein C-III is significantly affected.

The severity of morphological changes in patients with chronic pancreatitis leads to reduced levels of apolipoprotein A-I and C-III. We found

no significant association between of increased risk of myocardial infarction by apolipoprotein B to apolipoprotein A-I ratio with the progression of chronic pancreatitis severity.

Although reported lower apolipoproteins levels by endocrine dysfunction, diabetes mellitus does not appear to be a significant factor for all apolipoproteins.

Limitations

There are some limitations in our study: the patients were not followed-up, there was no assessment of the liver and we did not investigate the type of diabetes mellitus.

Conclusions

In the present study, we observe an increased CVR in the enrolled patients, who necessitate a change in lifestyle, smoking cessation, maintenance of optimal blood sugar levels, and correction of dyslipidemia. Men are at higher risk. Future long-term follow-up studies should verify the role of PERT in the prevention of CV events in patients with PEI. With respect to the progression of pancreatic diseases, the development of PEI, and the deterioration of the pancreatic structure, efforts should be made not only for PERT optimization but also for accurate assessment of patients' CVR. The evaluation of new markers such as apolipoproteins and routine lipid profiles would possibly benefit the strategies for the identification of patients at risk of CV events. A proper follow-up requires a multidisciplinary approach by a team of gastroenterologists, cardiologists, and endocrinologists.

Conflict of Interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Ethics Approval

The study was approved by the Ethics Committee of Medical University of Sofia, Sofia Bulgaria (Project Grant Young investigator 2015, No. 1-D/2015; and Project Grant 2016, No. 79/2016)

Informed Consent

All patients participated voluntarily in the study after the study protocol and informed consent had been explained properly by the investigator.

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Authors' Contributions

All authors contributed to the study.

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