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Trial of Cardiovascular Risk Factor Assessment and Transthoracic Echocardiography Results in Patients with Primary Antibody Deficiency

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ABSTRACT

The life expectancy and the risk of developing cardiovascular diseases in patients with inborn errors of immunity are systematically increasing.

The aim of the study was to assess cardiovascular risk factors and to evaluate the heart in echocardiography in patients with primary antibody deficiency (PAD). Cardiac echography and selected cardiovascular risk factors, including body mass index, sedentary lifestyle, nicotine, glucose, C-reactive protein, lipid profile, uric acid level, certain chronic diseases, and glucocorticoid use, were analyzed in 94 patients >18 years of age with PAD.

Of the patients,25.5% had a cardiovascular disease (mostly hypertension, 18%), 10.5% smoked, 17% were overweight, 14% were obese, and 15% were underweight. Abnormal blood pressure was found in 6.5% of the patients. Lipid metabolism disorders were found in 72.5% of in the studied cohort, increased total cholesterol (45.5%), non-high-density lipoprotein (HDL) (51%),

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low-density lipoprotein (LDL) (47%), and triglycerides (32%) were observed. Furthermore, 28.5% had a decrease in HDL and 9.5% had a history of hyperuricemia. The average number of risk factors was 5 ± 3 for the entire population and 4 ± 2 for those under 40 years of age. Elevated uric acid levels were found de novo in 4% of participants. In particular, 74.5% of the patients had never undergone an echocardiogram with a successful completion rate of 87% among those tested. Among them, 30% showed parameters within normal limits, primarily regurgitation (92.5%). New pathologies were identified in 28% of patients.

Prevention in patients with PAD, aimed at reducing cardiovascular risk, should be a priority.

Keywords: Echocardiography; Heart disease risk factors; Primary immune deficiency; Primary prevention; Primary antibody deficiency

INTRODUCTION

Cardiovascular risk is an assessment of the probable occurrence of cardiovascular disease or death from it (including complications and cardiovascular incidents such as myocardial infarction or stroke) over a specified period. The new European Society of Cardiology (ESC) guidelines recommend calculating cardiovascular risk based on the new SCORE2 and SCORE2-Older Persons (SCORE2-OP) tables. However, those apply only to potentially healthy individuals aged 40 to 89.[1]

Patients with primary immunodeficiencies, now called inborn errors of immunity (IEI), have an increased risk of infections, autoimmune diseases, and cancers.[2,3] Due to improvements in the diagnosis of IEI, the life expectancy of patients is being increased, and thus their risk of developing cardiovascular disease increases. Therefore, patients in this group should be evaluated in this regard and proper prophylaxis should be implemented. We analyzed patients with primary antibody defects (PAD) as they account for more than 50% of all IEI cases.

An important aspect related to primary cardiovascular prevention is endothelial dysfunction, which is a systemic disorder. Traditional cardiovascular risk factors, such as aging, gender, hypertension, smoking, hyperglycemia, and dyslipidemia, as well as emerging risk determinants, such as fetal factors, changes in the intestinal microbiome, clonal hematopoiesis, and air pollution, act synergistically, intensifying the adverse changes in vessels. In endothelial dysfunction, there is a reduction in nitric oxide (NO) bioavailability due to epigenetically sensitive dysregulation of the endothelial nitric oxide synthase (eNOS) gene and an increase in reactive oxygen species (ROS) in endothelial cells. Reducing modifiable risk factors may restore endothelial function via epigenetic-sensitive pathways capable of reducing inflammation and oxidative stress and increasing NO production.[4,5]

People with IEI often have additional unfavorable factors that increase cardiovascular risk, including frequent inflammation, autoimmunity, cancer, and treatment, such as long-term therapy with glucocorticosteroids.[2,3,6]

The aim of the study was to assess cardiovascular risk factors and perform an echocardiographic evaluation in patients with PAD.

MATERIALS AND METHODS

The study involved analysis of the results of selected cardiovascular risk factors (age, sex, body mass index [BMI], nicotinism, sedentary lifestyle, stress, lipid profile, glucose, C-reactive protein [CRP], uric acid levels, selected chronic diseases, autoimmunity, current or past long-term use of glucocorticosteroids). A transthoracic echocardiogram was also performed. The analyzed parameters were included in the typical care protocol for adult patients with PAD developed by the authors of the paper,[7] performed between June 1, 2021, and October 31, 2022. SCORE2 and SCORE2-OP were also hypothetically calculated to compare the index without comorbidities and factors present in patients. Inclusion criteria wereage18 years or older, diagnosis of IEI based on criteria of the European Society for Immunodeficiencies (ESID),[8] and informed consent to participate in the study. The analysis was performed on 94 patients treated at the immunology center in Bydgoszcz, Poland. All participants were indigenous inhabitants of Central Europe (Caucasian race). The exclusion criteria were failure to meet the eligibility

criteria and lack of consent to participate in the study. The study was approved by the Bioethics Committee of the Nicolaus Copernicus University in Toruń (KB 215/2022).

Age was assumed as a cardiovascular risk factor for men≥55 years of age and women≥60 years of age. The reference values for the BMI and laboratory tests are presented in the Supplementary Table 1.

The risk factor of premature cardiovascular disease in the family history was not taken into account, due to the lack of knowledge on this subject in most patients.

Blood sampling for testing, as well as blood pressure measurement, took place during routine follow-up visits.Measurements were made using an automatic blood pressure monitor using a double pulse wave algorithm, allowing to increase the quality of measurements by doubling the heart rate detection. The measurement was carried out after a 15-minute rest, in a sitting position, with the back supported. The blood pressure monitor cuffwas placed 2 to 3 cm above the cubital fossa. Blood pressure>140/90 mmHg was considered abnormal.

Results are presented as the arithmetic mean and standard deviation. Statistical analysis of correlations was performed using Pearson's test. The statistical significance of the results was calculated utilizing the *t*-statistic calculated from the coefficient value. The *p* values were considered statistically significant when *p* was lower than 0.05. Calculations were performed using MS Excel 2019 with the Analysis Toolpak add-in.

RESULTS

Medical History and Physical Examination

In the study group consisting of 94 patients, the average age of patients, at the time of the study, was 41.3±14.7 years, whereas 45 people (48%) were<40 years old. Women accounted for 57.5% (54 participants). The distribution of individual immunodeficiencies in the study population is delineated as follows: common variable immunodeficiency (CVID) in 30 patients (32%), unspecified hypogammaglobulinemia in 26 patients (28%), selective IgA deficiency in 12 patients (13%), deficiency of IgG subclasses in 12 patients (13%), selective IgM deficiency in 4 patients (4%), and agammaglobulinemia in 8 patients (4 X-linked and 4 autosomal recessive). Immunodeficiency associated with other specified major defects was observed in 2 participants (2%).

Among the participants, 63 individuals (67%) received immunoglobulin supplementation, with the majority choosing subcutaneous administration (62 patients [98.5%]) and a minority opting for intravenous administration (1 patients [1.5%]). Thirty patients (28%) had cardiovascular disease: the most common was hypertension in 17 patients (18%) and atherosclerosis in 10 (9,5%). The frequency of other conditions was the following: ischemic heart disease in 3 (3%), history of pulmonary embolism in 2 (2%), aortic valve regurgitation in 1 (1%), mitral valve regurgitation in 1 (1%), Wolff-Parkison-White syndrome in 1 (1%), history of ventricular arrhythmias in 1 (1%), history of myocardial infarction in 1 (1%), history of acute idiopathic pericarditis in 1 (1%), history of pericarditis in 1 (1%)), congestive heart failure in the course of left heart hypoplasia syndrome in 1 (1%) (additionally, this patient had a history of cardiac surgeries: Norwood procedure, Fontan procedure, left pulmonary artery angioplasty with stent implantation and history of hemorrhagic stroke).

Four (4%) patients had type 2 diabetes and 4 (4%) had steroid-induced diabetes.

Ten people (10.5%) admitted to smoking cigarettes (9 people smoke regularly, 1 occasionally) and 5 (5.5%) declared a history of nicotine dependence.

Fifty-one patients (54%) were of normal weight, 16 (17%) were overweight, 13 (14%) were obese, and 14 (15%) were underweight.

Abnormal blood pressure readings were found in 6 patients (6.5%), 2 of whom were diagnosed with de novo hypertension and the rest with poorly controlled hypertension.

A detailed analysis of the patient's history and physical examination are shown in Table 1, 2 and Supplementary Tables 2, 3 and 4.

Table 1. Detailed characteristics of patients

Parameter	Results, n (%)	
Sex	Female	54(57.5%)
	Male	40(42.5%)
Inborn errors of immunity	Common variable immunodeficiency	30(32%)
	Unclassified antibody deficiency	26(28%)
	Selective IgA deficiency	12(13%)
	IgG subclass deficiency	4(4%)
	X-linked agammaglobulinemia	4(4%)
	Autosomal recessive agammaglobulinemia	4(4%)
	Immunodeficiency associated with other specified major defects	2(2%)
Average age (years)		41.3±14.7
Age at diagnosis(years)		31.7±18.5
Age of symptom onset (years)		19.7±17.1
Average delay in diagnosis (years)		12.7±13.9
Immunoglobulin replacement therapy	Total	63(67%)
	Subcutaneous	62(98.5%)
	Intravenous	1(1%)
	Mean IgG concentration (mg/dL)	803.98±317.13
	Mean IgG dose (g/kg per month)	0.46±0.27
Infections		94(100%)
Antibiotic prophylaxis		1(1%)
Body mass index	Normal weight	50(53%)
	Overweight	17(18%)
	Obese	13(14%)
	Underweight	14(15%)
Smoking	Currently	10 (10.5%)
	Regularly	9(9.5%)
	Occasionally	1(1%)
	In the past	5(5.5%)

Table 1. Continued...

Cardiovascular diseases	Previously occurring	24(25.5%)
	Hypertension	
	for the entire study group	17(18%)
	for the group >40 years old	17(35%)
	Atherosclerosis	3(3%)
	Ischemic heart disease	3(3%)
	History of pulmonary embolism	2(2%)
	Aortic valve regurgitation	1(1%)
	Mitral valve regurgitation	1 (1%)
	Wolff-Parkison-Whitesyndrome	1(1%)
	History of ventricular arrhythmias	1(1%)
	History of myocardial infarction	1(1%)
	History of acute idiopathic pericarditis	1(1%)
	History of pericarditis	1(1%)
	Congestive heart failure (left heart hypoplasia syndrome)	1(1%)
	Recently diagnosed	
	Hypertension	1(1%)
	Atherosclerosis (visualized in chest and abdominal imaging studies)	7(7.5%)
	Abnormalities found in echocardiography	18(19%)
	Performed in the past	1(1%)
	Not previously performed	17(18%)
	(details reportedin Table 2)	
Diabetes	Previously occurring	
	Steroid-induced diabetes	4(4%)
	Type 2 diabetes	4(4%)
	Recently diagnosed	0(0%)
Autoimmunity	Total	28(30%)
	Autoimmune thyroid disease	7(7.5%)
	Inflammatory bowel disease	5(5.5%)
	Autoimmune hemolytic anemia	3(3%)
	Idiopathic thrombocytopenic purpura	*3(3%)*
	Vasculitis	3(3%)
	Rheumatoid arthritis	2(2%)
	Psoriasis	2(2%)
	Psoriatic arthritis	1(1%)
	Primary adrenal insufficiency	1(1%)
	Pernicious anemia	1(1%)
	Autoimmune hepatitis	1(1%)
	Sjogren's syndrome	1(1%)
	Celiac disease	1(1%)
	Grave's disease	1(1%)
	Myasthenia gravis	1(1%)
	Antiphospholipid syndrome	1(1%)

Table 1. Continued...

Chronic kidney disease		2(2%)
Lipid metabolism disorders	Previously occurring	31(33%)
	Only 5 patients (5.5%) had normal values in follow-up	68(72.5%)
	Recently diagnosed	43(45.5%)
	↑TC (mg/dL)	44(47%)
	↑LDL (mg/dL)	27(28.5%)
	↓HDL (mg/dL)	48(51%)
	↑non-HDL (mg/dL)	30(32%)
	↑TG (mg/dL)	
Hyperuricemia	Previously occurring	9(9.5%)
	Recentlydiagnosed	7(7%)
	persisted at follow-up	3 (3%)
	de novo	4 (4%)

TC: total cholesterol, LDL: low-density lipoprotein, HDL: high density lipoprotein, TG: triglycerides

Table 2. Analysis of cardiovascular risk factors

Parameter	**Result, n (%)**		
SCORE 2/SCORE2-OP*	45 (48%) not applicable (<40 years old)		
	49 (52%) calculated (⩾40 years of age)		
	10-year risk of cardiovascular events		
	• <5%		35(71.5%)
	• ⩾5 and<10%		13(26.5%)
	• ⩾10%		1(2%)
Mean number of risk factors	For the whole group		5±3
	For patients <40 years of age		4±2
	For patients ⩾40years of age		6±3
Analysis of individual risk factors	**Total**	**Patients <40 years of age**	**Patients ⩾40 years of age**
Age	16(17%)	0	16(32.5%)
Sex	40(42.5%)	23(51%)	17(34.5%)
Abnormal BMI	44(47%)	20(44.5%)	24(49%)
Smoking	10(10.5%)	4(9%)	6(12%)
Sedentary lifestyle	51(54%)	19(42%)	32(65.5%)
Diabetes	8(8.5%)	1(2%)	7(14.5%)
Lipid metabolism disorders	68(72.5%)	24(53.5%)	44(90%)
Chronic kidney disease	2(2%)	1(2%)	1(2%)
Cardiovascular diseases	27(28.5%)	4(9%)	23(47%)
Increased C-reactive protein	29(31%)	12(26.5%)	17(34.5%)
Hyperuricemia	13(14%)	5(11%)	8(16.5%)
Hyperglycemia	7(7.5%)	2(4.5%)	5(10%)
Autoimmunity	28(30%)	9(20%)	19(39%)
Long-term use of glucocorticoids	38(40.5%)	11(24.5 %)	27(55%)
Stress	94(100%)	45(100%)	49(100%)

* Hypotetical indicator, calculated for comparative purposes

Correlations in Lipid Profiles and Immunodeficiency-related Factors

Statistical analysis showed a statistically significant positive correlation between the total cholesterol concentration and the age of the patients, the age at which IEI was diagnosed, and the concentration of LDL, non-HDL, and triglycerides. For the last 3parameters, a strong positive correlation was found (Pearson correlation coefficients $r \geqslant 0.5$). The number of cardiovascular risk factors significantly and positively correlated with the age of patients, the age at which immunodeficiency was diagnosed, the age at which the first symptoms appeared, and the concentration of non-HDL and triglycerides. A significant negative correlation was found between the concentration of uric acid and HDL. The delay in diagnosis correlated significantly positively with the age of the patients, the age at which the diagnosis was made, and significantly negatively with the age at which the first symptoms of immunodeficiency appeared.The results of the statistical analysis are presented graphically in Table 3.

Echocardiography

Only 24 participants (25.5%) had a cardiac echo performed prior to the study. Nineteen patients (79%) had normal results, but 4 patients (21%) had mitral and/or tricuspid regurgitation that was still within normal limits, and 1 patient (5%) had a borderline left ventricular dimension in systole. Seventy patients (74.5%) had never undergone a cardiac echography. In this group, the test was performed successfully in 87% (61 patients). Of these, 72% (44 patients) had normal test results. However, 30% (13 patients) exhibited findings that were still within normal limits, including mitral, tricuspid, or aortic regurgitation in 92.5% (12 patients), a Chiari network in 15.5% (2 patients), false chordae tendineae in the left ventricular lumen in 7.5% (1 patient), and increased calcification of the aortic leaflets' edges in 7.5% (1 patient).

New pathologies were identified in 28% of the participants (17 people), with a detailed echocardiographic analysis provided in Table 4. The delay in diagnosis was calculated against the recommended examination frequency. For general cases, this is at least once every five years and for mild cardiovascular diseases, every 2 to 4 years. This section is organized with subheadings for clarity and provides a succinct yet precise description of the experimental results, their interpretations, and the conclusions that can be drawn.

Table 3. Pearson correlation coefficients (r) between measured parameters and clinical data of adult patients with primary antibody deficiency. Statistically significant results ($p< 0.05$) are shown in bold with the corresponding *p*value. The underlined results suggest a strong correlation ($r\geqslant0.5$), while the results written in bold without underlining suggest a moderate correlation ($0.3<r<0.5$).

	Age (years)	Age at diagnosis (years)	Age of symptom (years)	Delay in diagnosis (years)	BMI	TC (mg/dL)	LDL (mg/dL)	HDL (mg/dL)	non-HDL (mg/dL)	TG (mg/dL)	Glucose (mg/dL)	Uric acid (mg/dL)	CRP (mg/L)	SRF
Age (years)	**1**													
Age at diagnosis (years)	**0.922 ($p<0.0001$)**	**1**												
Age of symptom (years)	**0.654 ($p<0.0001$)**	**0.701 ($p<0.0001$)**	**1**											
Delay in diagnosis (years)	**0.419 ($p<0.0001$)**	**0.465 ($p<0.0001$)**	**-0.305 ($p=0.0013$)**	**1**										
BMI	**0.258**	**0.222**	**0.301 ($p=0.0031$)**	**-0.078**	**1**									
TC (mg/dL)	**0.304 ($p=0.0029$)**	**0.302 ($p=0.0039$)**	**0.159**	**0.205**	**0.164**	**1**								

Table 1. Continued...

LDL (mg/dL)	**0.188**	**0.167**	**0.101**	**0.097**	**0.150**	**0.897 (*p*<0.0001)**	**1**						
HDL (mg/dL)	**0.247**	**0.311 (*p*=0.0034)**	**0.260**	**0.093**	**0.035**	**0.389 (*p*=0.0001)**	**0.102**	**1**					
non-HDL (mg/dL)	**0.239**	**0.189**	**0.045**	**0.196**	**0.140**	**0.893 (*p*<0.0001)**	**0.933 (*p*<0.0001)**	**0.044**	**1**				
TG (mg/dL)	**0.251**	**0.193**	**0.014**	**0.240**	**0.223**	**0.509 (*p*<0.0001)**	**0.495 (*p*<0.0001)**	**-0.201**	**0.621 (*p*<0.0001)**	**1**			
Glucose (mg/dL)	**0.266**	**0.207**	**0.094**	**0.159**	**-0.004**	**-0.135**	**-0.121**	**-0.074**	**-0.091**	**0.021**	**1**		
Uric acid (mg/dL)	**-0.058**	**-0.068**	**-0.052**	**-0.026**	**0.260**	**-0.106**	**-0.020**	**-0.312 (*p*=0.0022)**	**-0.040**	**0.219**	**0.157**	**1**	
CRP (mg/L)	**0.031**	**-0.102**	**-0.017**	**-0.115**	**-0.063**	**-0.086**	**-0.083**	**-0.121**	**-0.022**	**0.061**	**-0.054**	**-0.231**	**1**
SRF	**0.489 (*p*<0.0001)**	**0.409 (*p*<0.0001)**	**0.317 (*p*=0.0008)**	**0.142**	**0.338 (*p*=0.0019)**	**0.251**	**0.290**	**-0.109**	**0.323 (*p*=0.0015)**	**0.330 (*p*=0.0012)**	**0.147**	**0.264**	**0.140**	**1**

BMI, body mass index; CRP, C-reactive protein; HDL, high-density lipoproteins; LDL, low-density lipoproteins; non-HDL, non-high-density lipoproteins; SRF, specific risk factor; TC, total cholesterol; TG, triglycerides.

Table 4. Detailed analysis of the echocardiographic examination

Examination	Echocardiography
Previously performed examinations	24 (25.5%)
Normal examinations	19 (79%) However, 4 patients (21%) showed mitral and/or tricuspid regurgitation that was still within normal limits, and 1 patient (5%) showed borderline left ventricular diameter in systole.
Abnormal examinations	5 (21%)
Pathologies found	Patient #7: Tricuspid aortic valve with mild marginal fibrosis, flaccid atrial septum; Patient #43: A single ventricle with right ventricular anatomy was visualized, moderate retrograde flow through the tricuspid valve, mild aortic regurgitation; Patient #57: Left atrial enlargement, thickened mitral leaflet margins, degeneratively altered with prolapse features to a depth of about 6 mm in relation to the mitral annulus, moderate/severe mitral return wave, exceeds half of the left atrium, moderate tricuspid retrograde flow wave; Patient #82: Marked left ventricular hypertrophy with features of impaired relaxation, tricuspid aortic valve, small atrophic left coronary leaflet, small tricuspid retrograde wave, separation of pericardial plaques in PLAX- up to 6mm behind the posterior wall of the left ventricle, up to 4mm in front of the right ventricle in diastole; Patient #87: Widening of the ascending aorta, enlargement of the dimensions of the left atrium and right heart cavities, hypertrophy of the left ventricular muscle, and increased saturation of the aortic leaflets.
Examination performed without delay	18 (75%)
Examination performed with delay	6(25%)
Delay(years)	3.16±1.6
Follow-up examinations	13(54%)
Normal examinations	8 (61.5%) However, 1 person (10%) showed a borderline dimension of the left ventricle in systole that was still within normal limits.
Abnormal examinations	5(38.5%)
New pathologies	1(7.5%) Patient #46: Enlargement of the dimensions of both atria, dilatation of the ascending aorta, hypertrophy of the left ventricular muscle, and separation of the pericardial layers.
Number of people who have never been tested	70 (74.5%)
Newly performed examinations	61 (87%)

Table 1. Continued...

Normal examinations	44 (72%)
	However, 13 patients (30%) showed still within normal limits: mitral and/or tricuspid and/or aortic regurgitation - 12 patients (92.5%), Chiari network - 2 people (15.5%), false chordae tendineae in the left ventricular lumen - 1 person (7.5%), increased calcification of the edges of the aortic leaflets - 1 person (7.5%).
Abnormal examinations	17 (28%)
Pathologies found	Left ventricular muscle hypertrophy - 5 (29.5%) Left atrial enlargement - 4 (23.5%) Aortic valve regurgitation - 2 (12%) Dilatation of the aortic root - 1 patient (6%) The flaccid middle part of the atrial septum with trace left-right leakage - 1 (6%), Mitral valve regurgitation - 2 (12%) Tricuspid valve regurgitation -1 (6%) Prolapse of the anterior leaflet of the mitral valve - 1 (6%) Flaccid mitral valve leaflets, during systole, protruding towards the left atrium, without features of prolapse - 1 (6%) Slight contractile dysfunction of the left ventricular muscle with preserved good ejection fraction - 1 patient (6%)

DISCUSSION

PADs account for more than 50% of all IEIs. Improvements in the diagnosis and the introduction of immunoglobulin supplementation for deficiencies that run the gamut of quantitative or qualitative IgG abnormalities have resulted in longer patient lifespans.[8]This is associated with an increase in the risk of noncommunicable diseases, which necessitates a change in the approach to the care of IEI patients, especially in terms of primary prevention involving cardiovascular risk reduction.

The center, under whose care patients were recruited into the study, remain the youngest immunology center in Poland. Therefore, the average time under the center's care was 3.75±3.31 years. It is also one of the 3 centers with the largest number of IEI patients under its care. In order to provide patients with the best possible care, especially in terms of primary prevention, standards of care for patients with PAD have been developed and implemented. As mentioned earlier, deficiencies of this type are most common. Therefore, the introduction of the standard of care protocols in a group of people with these disorders provides an opportunity to extend appropriate care to as many patients as possible. These protocols allow for the assessment of factors influencing cardiovascular risk, such as age, sex, use of addictive substances, BMI, comorbidities, lipid metabolism disorders, and hyperuricemia.[7]

Active development of the field of clinical immunology and education in this field hassignificantly increased the frequency of IEI diagnoses. Our research has shown that the delay in diagnosis is shorter when symptoms occur early, preferably in childhood. When symptoms appear in adulthood, this period is longer and is associated with more adverse cardiovascular risk factors.

Monitoring nutritional status is crucial in assessing cardiovascular risk. Capra ME et al. emphasize the role of habits and nutritional interventions in the prevention of cardiovascular disease from birth.[6] Excess body weight is associated with a higher risk of developing cardiovascular disease, diabetes, cancer, obstructive sleep apnea, respiratory problems, and degenerative changes in the musculoskeletal system. It is also associated with an increase in mortality from any cause.[10–12]

The problem of obesity in patients with PAD has so far been addressed in terms of immunoglobulin dosing or COVID-19 course.[13,14] Ruffner et al. emphasized that

the prevalence of underweight and obesity in primary immunodeficiencies is unknown, despite the described correlations between mentioned conditions and nutritional status.[15]Rahman et al. emphasize that nutritional status and heart failure have strong associations.[16] In addition, malnutrition also worsens the course of immune deficiency and heart disease and increases the risk of cardiovascular disease, while a proper diet can make a positive impact in this regard.[17]

There are no research papers in the literature analyzing the effect of smoking on cardiovascular risk in patients with PID. Several studies confirm that smoking increases the risk of gastric cancer in patients with CVID, or breast cancer in ataxia-telangiectasia gene carriers as compared to a group of non-smokers.[18,19] In a study conducted by van der Poorten et al. in 2018, a significant smoking history was reported by 38% of CVID patients.[18]In the analysis conducted by the authors of the following study, smoking was declared by 10.5% of patients, while 5.5% of patients declared a history of nicotine dependence, which is probably related to patients' greater awareness of smoking-related diseases. Regular follow-up and education in this regard should be routinely carried out, especially in patients with PID.

It is worth noting that abnormalities in lipid metabolism were found in more than 70% of patients. Of importance is not only hyperlipidemia which increases the risk of cardiovascular disease and ischemia of many organs (especially non-HDL), but also reduced HDL levels. HDL is the only fraction that has proven anti-inflammatory and cardioprotective effects.[20]An analysis by Andrade IGA et al. in CVID patients showed higher levels of oxidized LDL (LDLox) and lower levels of apolipoprotein A-I (Apo A-1) in CVID patients compared to controls, suggesting oxidative stress and cardiovascular risk.[21]

Elevated uric acid concentration can be an indicator of an active proliferative process, especially in patients with IEI.[22] Additionally, hyperuricemia is associated with oxidative stress, oxidation, DNA damage, production of inflammatory cytokines, and even cell apoptosis.[23] Chronic hyperuricemia is a risk factor for hypertension, metabolic syndrome, chronic kidney disease, and cardiovascular disease, as well as hyperlipidemia.[24] Therefore, regular monitoring of uric acid levels should be included in the care of patients with PID.

The analysis of risk factors showed that patients with PAD are a group of patients with increased cardiovascular risk. It is alarming that the average number of risk factors in the patients was 5±3 and was also high in the group of patients under 40 (the average number of risk factors was 4±2). The prevalence of hypertension in the group of patients with PAD over 40 years of age was 35% and is similar to the general population at this age in this region (34%).[25] Patients with IEI are also more prone to autoimmunity.[2,3] The problem of increased cardiovascular risk in autoimmune patients was raised by the European League Against Rheumatism (EULAR). A multidisciplinary task force made recommendations for cardiovascular risk prediction and management based on systematic literature reviews and opinions for vasculitis, systemic sclerosis, myositis, mixed connective tissue disease, Sjögren's syndrome, systemic lupus erythematosus, and antiphospholipid syndrome. The relationship between the use of glucocorticoids and cardiovascular risk was also emphasized. Recommendations can be used in the care of patients with IEI with concomitant autoimmunity.[6]

Cardiac complications in patients with PAD are rarely addressed in the literature. Transthoracic echocardiography seems to be the best non-invasive test that gives the most information about heart abnormalities. That is why this study was performed on patients. Electrocardiography, although it is a widely available, cheap, and simple test, has some limitations, for example in people with abnormal body weight, and this was found in as many as 47% of the analyzed patients. Functional tests also have limitations, especially since infections and chronic lung diseases, (e.g., interstitial lung disease) are common in immunocompromised patients. A study by Johnston et al. confirms that echocardiographic abnormalities are common in primary antibody deficiency, which is associated with delayed diagnosis and pulmonary complications.[26] It is important to remember that complications can also result from autoimmune diseases, past infections, and cardiovascular diseases associated with prolonging the life of patients, and therefore patients with IEI should also be evaluated for these. Cardiac evaluation should also become a standard due to the use of antibiotic prophylaxis prior to certain procedures involving tissue disruption, such as the prevention of infective endocarditis. It is also important in the selection of anti-cancer drugs.

Protocols for the care of PAD patients were not published until 2022. The purpose of the protocols is to

verify potential complications of immunodeficiency and accompanying chronic diseases. The recommended frequency of tests was introduced for regular screening of patients and prospective assessment. They were the first to take into account and enable the assessment of many cardiovascular risk factors and the assessment of transthoracic echocardiography. The analysis carried out is the first assessment of this type. The authors of the study are aware of the limitations of the work resulting from the limited number of participants and hope that soon there will be studies presenting the effects of implementing protocols that will enable comparison of larger numbers of patients with PAD.

Taking into account the increasing life expectancy of patients with IEI, primary prevention, in particular, aimed at reducing cardiovascular risk, should play a key role in the care of this group of patients.

In patients with IEI, the assessment of cardiovascular risk is difficult, among others: due to the presence of disturbances in the regulation of the immune system, which determine not only the course of the immunodeficiency itself but also the increased frequency of comorbidities and their more severe course. There are no tools to estimate the actual cardiovascular risk in this group of patients, therefore it is important to identify individual cardiovascular risk factors and their subsequent elimination.

It is also necessary to implement appropriate education, modify the diet, and depending on the estimated risk, implement pharmacological treatment in patients with PAD.

Cardiovascular risk factors, as well as transthoracic echocardiography, should be considered in the evaluation of patients with PID when establishing the diagnosis and should be monitored regularly.

Protocols of the standard of care for adult patients with PAD are a valuable tool to assess cardiovascular risk and implement primary prevention in this group of patients.

STATEMENT OF ETHICS

The study protocol was approved by the Ethics Committee at Collegium Medicum in Bydgoszcz (KB 215/2022).

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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