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The Concentration of Triglycerides is Significantly Associated with the Prevalence of Coronary Artery Disease in Pancreas Recipients with Type 1 Diabetes: A Cross-Sectional Study

ABSTRACT

Objective: Coronary artery disease (CAD) and its complications significantly affect the post-transplant prognosis in pancreas recipients. This study aimed to evaluate the associations between CAD and its major risk factors (RFs) and to identify the strongest modifiable predictor of CAD in potential pancreas recipients with type 1 diabetes (T1D).

Materials and methods: This is a prospective, cross-sectional study. Patients with T1D qualified for simultaneous pancreas-kidney transplantation or pancreas transplantation alone were enrolled. The diagnosis of CAD was based on invasive coronary angiography. The major cardiovascular RFs included in the analyses were hypertension, lipid profile, obesity, and smoking.

Results: The study population included 113 patients with a median age of 40 (35–46) years. The median duration of T1D was 26 years (23–32), and 61.9% of participants (n = 70) were on hemodialysis. CAD was found in 31 (27.4%) participants. Multivariate logistic regression analysis demonstrated that age (OR 1.159; 95% CI: 1.062–1.265, p = 0.001), the concentration of triglycerides (TG) (OR 4.534; 95% CI: 1.803–11.403, p = 0.001), and hemodialysis (OR 4.027; 95% CI: 1.13–14.358, p = 0.032) were independently associated with the prevalence of CAD in this cohort. Finally, the concentration of TG was the only modifiable RF that was independently associated with the prevalence of CAD.

Conclusions: Fasting TG levels were positively associated with the prevalence of CAD in potential pancreas recipients with T1D. The concentration of TG has the potential to serve as a modifiable RF or at least as an important biomarker in this group and should be included in the cardiological pre-transplant assessment.

Keywords: type 1 diabetes, triglycerides, pancreas transplantation, pancreas-kidney transplantation, coronary artery disease, risk factors

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Introduction

Pancreas transplantation is a well-established treatment method for selected patients with type 1 diabetes (T1D) [1]. The most common transplant methods are simultaneous pancreas-kidney transplantation (SPKT) and pancreas transplantation alone (PTA). Patients with severe diabetic nephropathy are qualified for SPKT, while patients with preserved kidney function are qualified for PTA. Both treatment options improve patients' prognoses, eliminate the need for exogenous insulin administration, and improve diabetes-related complications [2, 3].

Advances in surgical techniques and immunosuppressive protocols have contributed to excellent patient survival; however, cardio-cerebrovascular events remain one of the main reasons for death in the first year after transplantation [4]. Therefore, a precise cardiac evaluation of pancreas recipients is crucial to reduce peri-transplant complications. Considering the relatively long waiting time for the organ, the preoperative assessment should include both the patient's current cardiological status and the risk of developing coronary artery disease (CAD) in the next few years. The accelerated progression of atherosclerosis in T1D patients is mainly due to hyperglycemia and glycemic variability, but other cardiovascular risk factors (RFs) are also of great importance [5–7]. Hence, it is necessary to identify the factors that play the most significant role. This knowledge could be used to modify cardiovascular risk, thereby slowing the progression of atherosclerosis and decreasing perioperative risk.

Therefore, this study aimed to evaluate the prevalence of major cardiovascular RFs and to identify the most significant modifiable predictor of CAD in potential pancreas recipients with T1D.

Materials and methods

Study design and subjects

This prospective cross-sectional study population included pancreas transplant candidates with T1D who were referred for cardiological pre-transplant assessment and included both patients eligible for SPKT and PTA. Patients were prospectively enrolled from August 2018 to November 2023. The exclusion criteria for study participants were type 2 diabetes, severe valvular heart disease, heart failure, history of coronary heart disease or stroke, and changes in lipid-lowering and/or antihypertensive therapy within 3 months before the study entry.

Data collection

The following demographic and medical data were collected: age, sex, type of planned transplantation procedure, age at onset and duration of T1D, renal replacement therapy, and major risk factors for CAD (hypertension, smoking habit, dyslipidemia, obesity). Hypertension was defined as systolic blood pressure (SBP) >140 mmHg or diastolic blood pressure (DBP) > 90 mmHg and/or if a patient was on antihypertensive therapy before admission. Dyslipidemia was defined when TC > 4.9 mmol/L and/or TG > 1.7 mmol/L or if a patient was on lipid-lowering therapy [8]. Smoking was defined as active smoking in the last 5 years. All patients were rated for hypotensive and lipid-lowering therapy.

Height (m) and weight (kg) were measured with light clothes and without shoes. People on dialysis were weighed on a non-dialysis day. BMI was calculated as weight divided by height squared. Obesity was defined as a BMI $\geq$ 30 kg/m^2.

SBP and DBP were measured on 3 consecutive days between 8 and 9 a.m. using an automatic oscillometric blood pressure monitor. Measurements were taken in a seated position after 10 min of rest, and each measurement was repeated 3 times. The mean value of SBP and DBP was calculated as an average of 3 measurements over 3 days.

A commercially available analyzer (Beckman Coulter Inc., Brea, CA, USA) was used to measure the concentrations of HbA1C, serum creatinine, total cholesterol (TC), high-density lipoprotein (HDL), and triglycerides (TG) from fasting blood samples. The concentration of low-density lipoprotein-cholesterol (LDL-C) was calculated using the Friedewald formula: LDL-C = TC – HDL-C – TG/2.2 (mmol/L) [9]. Non-high-density lipoprotein-cholesterol (n-HDL-C) was calculated as n-HDL-C = TC – HDL-C.

The diagnosis of CAD was based on noninvasive and invasive tests. Patients with severe chronic kidney disease (eGFR < 30 mL/min/1.73 m^2) and long T1D duration ($\geq$ 20 years) were directly subjected to invasive coronary angiography. The other patients were referred for noninvasive tests, including an exercise stress test on a treadmill or a pharmacological stress test using dipyridamole 99 mTc-sestamibi single-photon emission computed tomography (SPECT) for patients with physical limitations. Patients with positive or inconclusive results of noninvasive tests were uniformly subjected to invasive coronary angiography. Invasive coronary angiography was performed with a Philips Allura Xper DF20 X-ray system using standard diagnostic catheters. Vascular access through the radial artery was used. CAD was defined as obstructive coronary disease based on the detection of at least one stenosis > 50% in at least one of the major coronary arteries.

Table 1. Baseline Characteristics of the Study Population Stratified by CAD

	Total (n = 113)	CAD (n = 31)	No CAD (n = 82)	P-value
Age [years]	40 (35–46)	44 (38–51)	38.5 (34–44)	0.005
Sex (male)	49 (43.3%)	17 (54.8%)	32 (39%)	0.1
Age of diagnosis of T1D [years]	13 (8–17)	14 (9–20)	12 (8–16)	0.2
Duration of T1D [years]	26 (23–32)	27 (24–35)	25 (22–31)	0.07
Hemodialysis	70 (61.9%)	26 (83.9%)	44 (53.7%)	0.004
Duration of hemodialysis [months]	18 (9–28)	22.5 (11–28)	14 (8–27)	0.25
BMI [kg/m^2]	22.95 (20.8–25.4)	23.6 (20.6–26.7)	22.8 (20.8–24.7)	0.4
HbA1c [%]	7.66 (6.95–8.42)	7.79 (7.2–8.64)	7.47 (6.82–8.4)	0.2

Categorical variables are presented as numbers and percentages (%), and continuous variables are presented as median with interquartile range (IQR)
BMI — body mass index; CAD — coronary artery disease; HbA1c — glycated hemoglobin; T1D — type 1

Statistical analysis

Continuous data were presented as median with interquartile range (IQR) and categorical variables as numbers and percentages of distribution. The normality of the data distribution was tested using the Shapiro-Wilk test. The participants were categorized into 2 groups by CAD diagnosis. For parameters not having normal distributions, statistical analyses were based on non-parametric tests. The Mann-Whitney U test was used to compare continuous variables between 2 groups, and Fisher's exact test or the chi-squared test was used to examine the significance of differences between categorical variables.

Multivariate logistic regression analysis was used to test the combined relationship between the prevalence of CAD and cardiovascular RFs. The multivariable logistic regression model included all modified RFs that were significant in the univariate analysis and potential confounding factors. The multivariate model used the backward stepwise elimination method, starting with a model including all the variables. The results were presented as odds ratio (OR) with a 95% confidence interval (CI).

Statistical analyses were performed using Statistica version 13.3 (TIBCO Software Inc., California, USA). For all statistical analyses, a p-value < 0.05 was considered significant.

Results

Participants' characteristics

The study population included 113 patients, of whom 29 patients (25.7%) were qualified for PTA and 84 patients (74.3%) for SPKT. The median age of the population was 40 (35–46) years, and 64 patients (56.7%) were female. The median duration time of T1D was 26 (23–32) years, and most of the study group (n = 93; 82.3%) were participants with long-standing diabetes (over 20 years). Above two-thirds of patients (n = 70; 61.9%) were on hemodialysis.

Invasive coronary angiography was performed in 107 patients (94.7%). The other patients (n = 6; 5.3%) had negative results of stress tests and were excluded from invasive assessment. Finally, CAD was found in 31 participants (27.4% of the entire cohort). The baseline characteristics of the enrolled patients stratified by CAD are illustrated in Table 1. In general, patients with CAD were older [44 years (38–51) vs. 38.5 years (34–44), p = 0.005] than patients without CAD, and the majority were on hemodialysis [26 (83.9%) vs. 44 (53.7%), p = 0.004]. The duration of renal replacement therapy and diabetes-specific RFs (age of diagnosis, duration of T1D, level of HbA1c) did not have any significant associations with the prevalence of CAD.

Assessment of cardiovascular RFs

The prevalence of traditional cardiovascular RFs was very high. Most participants (n = 81; 71.7%) had 2 to 3 major RFs (Tab. 2). However, there was no significant association between the number of RFs and the prevalence of CAD. As shown in Table 3, hypertension and dyslipidemia were the most common RFs in the study group (n = 96; 85% and n = 80; 70.8%, respectively). Active smoking was declared by 31 participants (27.4%) with a median of 13 pack-years (6–18.3) of smoking exposure. Obesity was the least common RF in the study group.

Table 2. The Association Between the Number of Major Modifiable Cardiovascular RFs and the Prevalence of CAD

Number of RFs	Total (n = 113)	CAD (n = 31)	No CAD (n = 82)	P-value
0	2 (1.77%)	0	2 (2.4%)	0.6
1	10 (8.85%)	2 (6.45%)	8 (9.76%)	
2	43 (38.05%)	10 (32.26%)	33 (40.2%)	
3	38 (33.62%)	12 (38.7%)	26 (31.7%)	
4	20 (17.7%)	7 (22.6%)	13 (15.85%)	

Major cardiovascular risk factors included: hypertension, dyslipidemia, smoking, and obesity; categorical variables are presented as numbers and percentages (%)
CAD — coronary artery disease; RFs — risk factors

Table 3. Characteristics of the Major Modifiable Cardiovascular RFs

	Total (n = 113)	CAD (n = 31)	No CAD (n = 82)	P-value
Hypertension	96 (85%)	30 (96.8%)	66 (80.5%)	0.04
ACEi/ARBs	55 (48.7%)	23 (74.2%)	32 (39.0%)	0.001
Calcium channel blockers	70 (61.9%)	21 (67.7%)	49 (59.8%)	0.5
Beta-blockers	61 (54.0%)	22 (71.0%)	39 (47.6%)	0.03
Diuretics	57 (50.4%)	18 (58.1%)	39 (47.6%)	0.4
Alpha-blockers	20 (17.7%)	6 (19.3%)	14 (17.1%)	0.8
Centrally acting agents	6 (5.3%)	2 (6.45%)	4 (4.9%)	0.7
SBP [mmHg]	132 (122–146)	144 (129–158)	130.5 (122–138)	0.0002
DBP [mmHg]	77 (71–84)	80 (72–88)	76 (71–83)	0.04
Dyslipidemia	80 (70.8%)	25 (80.65%)	55 (67.1%)	0.2
Statin users	49 (43.36%)	17 (54.8%)	28 (34.1%)	0.05
Statin dose [mg]	20 (10–40)	20 (10–20)	20 (20–40)	0.06
TC [mmol/L]	4.7 (3.8–5.6)	5 (3.5–5.7)	4.7 (3.9–5.6)	0.97
LDL-C [mmol/L]	2.5 (2–3.1)	2.7 (1.8–3.2)	2.5 (2.1–3.1)	0.75
HDL-C [mmol/L]	1.4 (1.2–1.8)	1.3 (1.2–1.4)	1.5 (1.3–1.9)	0.01
non-HDL-C [mmol/L]	3.1 (2.5–3.8)	3.1 (2.5–3.7)	3.2 (2.3–4.1)	0.7
TG [mmol/L]	1.3 (1–1.8)	1.8 (1.4–2.1)	1.2 (1–1.7)	0.00003
Obesity	6 (5.3%)	3 (9.7%)	3 (3.7%)	0.3
Current smoking	31 (27.4%)	11 (35.5%)	20 (24.4%)	0.2
Smoking exposure [pack-years]	13 (6–18.3)	13 (5–20)	12.75 (7–17.5)	0.94

Categorical variables are presented as numbers and percentages (%), and continuous variables are presented as median with interquartile range (IQR)
ACEi — angiotensin-converting enzyme inhibitors; ARB — angiotensin receptor blockers; CAD — coronary artery disease; DBP — diastolic blood pressure; HDL-C — high-density lipoprotein cholesterol; LDL-C — low-density lipoprotein cholesterol; RFs — risk factors; SBP — systolic blood pressure; TC — total cholesterol; TG — triglycerides

Associations between CAD and RFs

Associations between the prevalence of CAD and cardiovascular RFs of interest are shown in Table 3. There were no significant between-group differences in the prevalence of hypertension, dyslipidemia, smoking, or obesity. However, significant differences were found in specific lipid parameters and blood pressure values. Both SBP and DBP were significantly higher in patients with CAD than in patients without CAD (144 mmHg [129–158] vs. 130.5 mmHg [122–138], p = 0.0002, and 80 mmHg [72–88] vs. 76 mmHg [71–83], p = 0.04, respectively). The concentration of TG was significantly higher (1.8 mmol/L [1.4–2.1] vs. 1.2 mmol/L [1–1.7], p = 0.00003), while HDL-C was significantly lower (1.3 mmol/L [1.2–1.4] vs.1.5 mmol/L [1.3–1.9], p = 0.01) in patients with CAD than in the other participants. There were no significant differences in other lipid parameters (TC, LDL-C, non-HDL) between patients with and without CAD.

Table 4. Logistic Regression Analyses of Cardiovascular RFs Associated with CAD

Univariate logistic regression analysis			
Variable	**OR**	**95% CI**	**P-value**
Sex (male)	0.576	0.179–1.849	0.35
Age [years]	1.135	1.040–1.240	0.005
Smoking	0.668	0.203–2.198	0.5
Triglycerides [mmol/L]	4.127	1.831–9.299	0.001
Systolic blood pressure [mmHg]	1.058	1.027–1.09	0.0002
Diastolic blood pressure [mmHg]	1.057	1.008–1.107	0.021
Hemodialysis	4.491	1.57–12.846	0.005
Statins using	1.053	0.346–3.209	0.92
Multivariate logistic regression analysis			
Age [years]	1.159	1.062–1.265	0.001
Triglycerides [mmol/L]	4.534	1.803–11.403	0.001
Hemodialysis	4.027	1.13–14.358	0.032

The multivariate logistic regression analysis model included all modified RFs that were significantly different in the univariate analysis (TG, SBP, DBP) and potential confounding factors (sex, age, smoking, hemodialysis, HDL-C, statins using)
CAD — coronary artery disease; CI — confidence interval; OR — odds ratio; RFs — risk factors

Associations of various cardiovascular RFs for CAD are presented in Table 4. In the univariate logistic regression analysis, age (OR 1.135; 95% CI: 1.040–1.240, p = 0.005), the concentration of TG (OR 4.127; 95% CI: 1.831–9.299, p = 0.001), SBP (OR 1.058; 95% CI: 1.027–1.09, p = 0.0002), and DBP (OR 1.057; 95% CI: 1.008–1.107, p = 0.021), and hemodialysis (OR 4.491; 95% CI: 1.57–12.846, p = 0.005) were significantly associated with CAD.

The multivariate analysis model included all modified RFs that were significantly different in the univariate analysis (TG, SBP, DBP) and potential confounding factors (sex, age, smoking, hemodialysis, HDL-C, statin use). The multivariate analysis demonstrated that age (OR 1.159; 95% CI: 1.062–1.265, p = 0.001), the concentration of TG (OR 4.534; 95% CI: 1.803–11.403, p = 0.001), and hemodialysis (OR 4.027; 95% CI: 1.13–14.358, p = 0.032) were independently associated with the prevalence of CAD in the presented cohort. Finally, the concentration of TG was the only modifiable RF independently associated with the prevalence of CAD in the entire cohort.

Discussion

The study included potential pancreas recipients referred to our center for cardiological pre-transplant assessment. The vast majority were patients with long-standing diabetes and many complications, including hemodialysis.

Multivariate analysis demonstrated that age, hemodialysis, and TG levels were independently associated with the prevalence of CAD in potential pancreas recipients with T1D. Higher values of these parameters were significant predictors of CAD, suggesting that older patients, those undergoing hemodialysis, and those with higher TG levels have a higher risk of CAD.

The most impressive result of this study is that the concentration of TG was the only modifiable RF independently associated with the prevalence of CAD. When the concentration of TG increased by 1 mg/dL, the odds of having CAD increased 4.5-fold.

Our study results demonstrated the high prevalence of CAD in pancreas recipients. Obstructive CAD was revealed in 27.4% of participants. Data from other researchers have shown very divergent results, and the incidence of CAD ranged from 19 to 71.7%, depending on the study population and the criteria for CAD diagnosis [10–12]. The high prevalence of CAD in pancreas transplant recipients justifies the multifactorial approach to identifying and controlling the most important modifiable cardiovascular RFs.

Additionally, we demonstrated that hemodialysis was independently associated with the prevalence of CAD in the presented cohort. HD increased the odds of having CAD 4.03-fold. In this regard, our results are in line with the results from other researchers suggesting a link between diabetic nephropathy and CAD in T1D patients. According to Tuomilehto et al. [13], the presence of nephropathy in T1D patients increased the relative risk for cardiovascular disease 10.3-fold. Giménez-Pérez et al. [14] demonstrated that decreased GFR and elevated albumin/creatinine ratio were both strongly associated with a first cardiovascular event in T1D patients and should be considered when estimat-

ing CV in primary prevention measures. The results from Harjutsalo et al. [15] also suggest that a higher degree of kidney disease increased the risk of CAD in T1D patients. Moreover, Oliveira et al. [16] assessed CAD in 20 hemodialyzed T1D patients using quantitative invasive coronary angiography and intravascular ultrasound. They found 29 lesions in 15 patients, of which 50% were significant (≥ 70% stenosis), even though the patients were asymptomatic. Additionally, subclinical CAD was present in all coronary arteries. Furthermore, according to Kim et al. [17], patients subjected to SPK were at higher risk of CAD among all pancreas recipients. After multivariable adjustment, the odds of any cardiovascular complication in the SPK group were significantly higher than in patients subjected to solitary pancreas transplantation (OR 1.48, 95% CI 1.21 to 1.80, p = 0.01). Moreover, there was a robust association between diabetic nephropathy and dyslipidemia [18]. Their findings may partly explain the results we observed.

The key finding of the present study is the high prevalence of traditional cardiovascular RFs (hypertension, dyslipidemia, smoking, obesity) and the lack of any significant associations between them and the prevalence of CAD. However, significant between-group differences were found in specific blood pressure values and lipid parameters. Both SBP and DBP were significantly higher in patients with CAD than in patients without CAD. The concentration of TG was also significantly higher in patients with CAD. It can, therefore, be assumed that the degree of control of a given risk factor is more important than the fact of having it. The achievement of therapeutic goals in cardiovascular RFs is probably crucial in decreasing the risk of CAD.

In the present study, the concentration of TG was significantly and independently associated with the prevalence of CAD. In observational studies, a higher concentration of TG was also significantly associated with the increased risk of CAD in the general population [19, 20]. Moreover, researchers from the PROVE IT-TIMI 22 trial demonstrated that higher concentrations of TG were associated with atherosclerotic cardiovascular disease independently of LDL-C levels [21]. The authors of the aforementioned research suggested that achieving low TG should be an additional consideration beyond low LDL-C in patients after ACS. In contrast to these results, several trials failed to prove that lowering the concentration of TG decreased the risk for CAD [22]. Presumably, for this reason, guidelines for many years ignored elevated TG, focusing on lowering LDL-C to reduce the risk of atherosclerosis. The therapy to lower TG levels might only be considered in high-risk patients when TGs are more than 2.3 mmol/L [23]. For some time, researchers have noticed that in statin-treated patients, the risk of cardiovascular events increased with a higher concentration of TG, even when LDL-C was at the target level [24, 25]. That is in line with results from Hero et al. [26], who demonstrated in 30,778 people with T1D that LDL-C was not a good predictor of cardiovascular disease. New insights suggest that elevated TG-rich lipoproteins are associated with the residual risk of atherosclerotic cardiovascular disease [27, 28]. Furthermore, there is evidence from genetic studies demonstrating that elevated TG-rich lipoproteins are causally associated with atherosclerotic cardiovascular disease [29, 30]. A cause-and-effect relationship between elevated triglyceride-rich lipoproteins and atherosclerosis was independent of low HDL cholesterol levels. Recent research based on Mendelian randomization studies also supports a causal relationship between plasma TG levels and atherosclerotic cardiovascular disease, including CAD (OR 1.33, 95% CI 1.24–1.43, p = 2.47 × 10^−13) [31]. The strong association between TG and CAD we observed was consistent with prior studies in T1D patients [6, 32, 33]. There are many potential mechanisms to explain the relationship between CAD and TG. The degradation products of TG-rich lipoproteins elicited cytotoxicity and apoptosis in human macrophages and endothelial cells, leading to an atherosclerotic process [34]. Furthermore, they increased the expression of macrophage inflammatory proteins, adhesion molecules, and coagulation factors (e.g., tumor necrosis factor-α, interleukin-1β, monocyte chemotactic protein-1, intercellular adhesion molecule-1) that lead to atherosclerosis [35, 36]. Finally, there is evidence from the Mendelian randomization approach on the causal relationship between elevated triglyceride-rich lipoproteins and low-grade inflammation [37]. It is worth noting that Tolonen et al. [38] observed that the association between CAD and TG was particularly observed at a lower concentration of TG. According to these authors, the TG cutoff point for predicting the occurrence of CAD in T1D was 0.94 mmol/L. The increasing importance of the link between TG and CAD was also seen by the authors of the latest guidelines, who suggested moderately increased fasting TG levels (more than > 1.7 mmol/L) as an indication for treatment, which should aim for TG levels less than 1.1 mmol/L [8]

Taken together, our findings strongly support intensive TG control in T1D patients qualified for pancreas transplantation. Current recommendations should be reconsidered to capture and minimize the residual cardiovascular risk in potential pancreas recipients with T1D.

Limitations

Our study has some limitations. The 2 main limitations are due to the application of a cross-sectional approach. First, the risk factors were measured only once, so the observed associations represented only a single-point estimate. Second, the results did not allow for establishing a causal relationship, which makes it impossible to say whether the high level of TG is a cause, an effect, or a marker of CAD. The third limitation is the small size of the group, which is due to the small number of patients referred for pancreas transplantation in Poland. Another limitation is the use of statins and antihypertensive drugs, which may have confounded the presented relationships. Nonetheless, the great value of our study is that the presented results reflect daily medical practice, and therefore the conclusions could be adopted for routine pre-transplant management.

Conclusions

Fasting TG levels were positively associated with the prevalence of CAD in potential pancreas recipients with T1D. The concentration of TG has the potential to serve as an important modifiable RF or at least as an important biomarker in this group and should be included in the cardiological pre-transplant assessment. Further research is needed to understand the mechanisms of the relationship between TG and CAD and develop more effective prevention and treatment methods.

Article information

Data availability statement

Raw data supporting the conclusions of this article will be made available by the corresponding author upon reasonable request, in accordance with the policy of the authors' institutions.

Ethics statement

The study was conducted according to the Declaration of Helsinki. The study protocol was approved by the local Bioethics Committee at the Medical University of Warsaw, Poland (no. KB/115/2018). All the patients enrolled signed an informed consent form to participate in the study.

Author contributions

Małgorzata Buksińska-Lisik: conceptualization, methodology, acquisition of data, analysis and interpretation of data, investigation, project administration, writing — original draft preparation, review, and editing. Przemysław Kwasiborski: analysis and interpretation of data, writing — original draft preparation. Paweł Skrzypek: acquisition of data. Artur Mamcarz: critical revision of the manuscript for important intellectual content. Wojciech Lisik: acquisition of data, critical revision of the manuscript for important intellectual content. All authors approved the final version of the submitted manuscript.

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Conflict of interest

The authors declare no conflict of interest.

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