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The Silesia Diabetes-Heart Project

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Diabetic Peripheral Neuropathy is Associated With Diabetic Kidney Disease and Cardiovascular Disease: The Silesia Diabetes-Heart Project

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Abstract: Microvascular complications of diabetes seem to be clustered and put patients at higher risk of developing cardiovascular disease (CVD). This was a questionnaire-based study designed to screen for the presence of diabetic peripheral neuropathy (DPN), defined as the score in the Michigan Neuropathy Screening Instrument (MNSI) above 2, and to evaluate its association with other complication of diabetes, including CVD. There were 184 patients included into

The authors declare no conflict of interest.

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the study. The prevalence of DPN in the study group was 37.5%. The regression model analysis revealed that the presence of DPN was significantly associated with the presence of diabetic kidney disease (DKD) ($P = 0.0034$;) and patient's age ($P < 0.0001$). Thirty-four patients (49.3%) with MNSI score >2 were diagnosed with CVD in comparison to 24 (20.1%) subjects with MNSI score ≤ 2 ($P = 0.00006$). In case of having one diabetes complication diagnosed, it is important to screen for others, including macrovascular ones. (Curr Probl Cardiol 2023;48:101726.)

Introduction

Diabetes mellitus is considered an epidemic of the 21th century. It is estimated that the global prevalence of diabetes will rise from 537 million adults (aged 20-79) in 2021 to 643 million in 2030 and 783 million by 2045. More than 6 million people died because of diabetes in year 2021, which can be translated into an alarming statement of 1 death occurring every 5 seconds. Diabetes mellitus is also a very costly disease for health care systems and it is estimated that financial outlays on diabetes management increased by over 300% during the last 15 years.[1] In association with the growing number of people with diabetes mellitus increasing prevalence of both macrovascular and microvascular complications is observed. The burden of chronic complications of diabetes is not only a problem for patients whose life quality and expectancy is decreased but also for the medical health care systems as their treatment on advanced stages is costly.[2-4]

One of the most common microvascular complication of diabetes is diabetic peripheral neuropathy (DPN).[5] The well-recognized risk factors for DPN are hyperglycemia,[6] dyslipidemia and hypertension.[7,8] They lead to DPN mainly through inflammation, oxidative stress, sorbitol and advanced glycation end products accumulation.[9,10] Besides, lifestyle-related traits such as body weight management, diet and physical activity play a significant role in DPN development.[11-13] DPN is the major trigger factor for diabetic foot (including Charcot neuroarthropathy and foot ulceration) which are the main reasons for undaunted lower-limb amputations.[14] The risk of amputation in patients with diabetes is estimated to be more than 25 times greater than in case of people without carbohydrates disorders.[15]

Diabetes itself leads to a 2-4 times higher cardiovascular risk in comparison with adults without carbohydrates disorders.[16] Besides, the

presence of DPN is associated with an even greater increase in cardiovascular diseases (CVD) occurrence[5,17-19] and cardiovascular disease is still the main cause of death among patients with diabetes.[17] DPN constitutes a variety of syndromes associated with the nervous system involvement and ranging from bilateral, symmetric neuropathic pain or an increased risk of falls to foot ulceration.[18] DPN becomes a serious problem, as the cost of health care keeps rising and accounts for an expenditure equivalent to the combined cost of prostate, lung, and breast cancers according to the National Health Service in United Kingdom.[20] The landmark UKPDS (The UK Prospective Diabetes Study) showed that intensive glucose control from the very onset of diabetes may be a preventive strategy both for micro - and macrovascular complications.[21] Unfortunately, significant numbers of patients does not meet the glycemic target even though there is much improvement in diabetes care in terms of new antidiabetic drugs and blood glucose monitoring technologies since the UKPDS study.[22] Moreover, early detection of DPN can be limited since the potential of neuropathy screening is underused in primary healthcare providers[23] and first symptoms of DPN might be overlooked by patients struggling with the loss of sensation.[24] It is estimated that DPN affects 8-75% of people diagnosed with diabetes.[25-30]

These high differences in prevalence of DPN in diabetic patients between multiple sources may be caused by various criteria for the diagnosis of DPN applied.[5] The diagnostic assessment of neuropathy varies widely and is mostly based on medical history and physical examination evaluating vibration foot sense, temperature or pinprick sensation and foot ulcer.[18] There are also scored clinical instruments usually used in research projects, such as the Michigan Neuropathy Screening Instrument, the Neuropathy Symptom Score and the Neuropathy Disability Score or the Neuropathy Impairment Score (NIS).[5,18] The MNSI was proposed in 1994 for the first time.[31] Since than it was used in many key clinical trials, among others the Action to Control Cardiovascular Disease in Diabetes (ACCORD),[32] the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC)[33] and the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2).[34] Therefore, its clinical usefulness is well established and therefore it was used in our study.

Guidelines for diabetes care, proposed both by the American Diabetes Association and European Association for the Study of Diabetes, indicate the necessity of screening for DPN annually in patients diagnosed with diabetes.[35,36] Early detection of neuropathy may be a prognostic factor for the progression of other complications due to the fact that there is a

possible correlation among microvascular complications, which may also increase the risk of macrovascular complications in a synergistic way.[37]

Diabetic kidney disease (DKD) is another chronic microvascular complication of diabetes and the major cause of end stage chronic kidney disease. However, the majority of deaths in the course of diabetes are caused by CVD which precede the stage of DKD when renal replacement therapy is already needed. DKD may affect up to 40% of patients with diabetes.[38-40] Among patients with type 1 diabetes mellitus (T1DM) DKD typically develops after at least 10 years of the disease, however in patients with type 2 diabetes mellitus (T2DM) it might be present at the time of diagnosis.[41] Structural changes underlying the pathogenesis of DKD result in the clinical manifestations useful in the diagnosis, such as albuminuria, proteinuria and/or decreased glomerular filtration rate.[42] According to the recommendations of American Diabetes Association and European Association for the Study of Diabetes, screening for DKD should be performed annually in patients diagnosed with diabetes.[35,36] For patients with T2DM it should be performed at the moment of diagnosis, and for T1DM ones after 5 years from the diabetes onset.[41] Screening should be performed by determining the urinary albumin-to-creatinine ratio (UACR) in a random spot urine collection[43,41] and estimated glomerular filtration rate (eGFR) calculated on the basis of serum creatinine concentration transformed by a validated formula (preferable the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[43,41] Elevated UACR is defined as $\geq$30 mg/g. DKD might be diagnosed on the basis of UACR (2 of 3 specimens collected within a 3- to 6-month period) and/or reduced eGFR $<$60mL/min/1.73m2 together with the absence of signs and symptoms which could be primarily caused by other kidney damage.[41] Furthermore, there is some evidence that patients with microvascular complications are at higher risk of developing cardiovascular events.[37] Also, these microvascular complications seem to be clustered, especially in case of poor glycemic control and longer duration of diabetes.[44]

Since there are some data indicating that DKD may be linked to other diabetic complications,[45] we investigated whether DPN is associated with DKD and other complications of diabetes as a part of the Silesia Diabetes-Heart Project.

Patients and Methods

This was a questionnaire-based study designed to screen for the presence of DPN in consecutive patients hospitalized in the Department of

Internal Medicine, Diabetology, and Nephrology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia in Katowice (Poland) and in the Department of Internal Diseases, Allergology, Endocrinology and Gastroenterology, Institute of Medical Sciences, University of Opole (Poland). Moreover, we also intended to assess the co-occurrence of DPN with other complication of diabetes. The study is a part of a larger prospective trial called the Silesia Diabetes-Heart Project (ClinicalTrials.gov Identifier: NCT05626413).

The Inclusion and Exclusion Criteria

The inclusion criteria were as follows: 18 years of age or above; T1DM of minimum 5 years of duration or T2DM of any duration. The exclusion criteria were as follows: T1DM duration shorter than 5 years, other types of diabetes than T1DM and T2DM, diagnosed or suspected polyneuropathy of origin other than diabetes (such as Guillain-Barre syndrome, cervical lumbar lesions), malignant neoplasms, severe infections, acute metabolic disorders, excessive alcohol consumption, lack of patient's consent to participate in the study. We also excluded woman who were pregnant at the time of the study.

The Michigan Neuropathy Screening Instrument

The presence of DPN was assessed with the Michigan Neuropathy Screening Instrument (MNSI) composed of 2 parts: a 15-item questionnaire and a lower extremity examination involving the assessment of the appearance of feet, presence of ulceration, vibratory sensation, tactile sensitivity and ankle reflexes.[31] The questionnaire consists of a set of 15 questions related to the feeling in patients' legs and feet.

The exact questions in the MNSI are as follows:

1. Are your legs and/or feet numb? (yes / no)
2. Do you ever have any burning pain in your legs and/or feet? (yes / no)
3. Are your feet too sensitive to touch? (yes / no)
4. Do you get muscle cramps in your legs and/or feet? (yes / no)
5. Do you ever have any prickling feelings in your legs or feet? (yes / no)
6. Does it hurt when the bedcovers touch your skin? (yes / no)
7. When you get into the bath or shower, are you able to tell the hot water from the cold water? (yes / no)
8. Have you ever had an open sore on your foot? (yes / no)
9. Has your doctor ever told you that you have diabetic neuropathy? (yes / no)

10. Do you feel weak all over most of the time? (yes / no)
11. Are your symptoms worse at night? (yes / no)
12. Do your legs hurt when you walk? (yes / no)
13. Is the skin on your feet so dry that it cracks open? (yes / no)
14. Are you able to sense your feet when you walk? (yes / no)
15. Have you ever had an amputation? (yes / no)

For Questions 7 and 13 were reversed scored than the others.

In this study DPN was defined as the MNSI score of >2.[33] The Polish version of the questionnaire was used for the study purpose.

Patient's Medical History Collection

Data about patient's medical history such as diabetes type, age, diabetes duration, body mass index (BMI), the hemoglobin A1c (HbA1c) HbA1c value, the occurrence of DKD, diabetic retinopathy (DR), and CVD documented in the patients' medical history were collected. BMI was determined by dividing patient's weight in kilograms by squared height. HbA1c was determined as a part of routine laboratory test results during hospitalization. HbA1c was measured using a high-performance liquid chromatography method (HPLC) and the results were expressed in the National Glycohemoglobin Standardization Program/Diabetes Control and Complications trial units.[46] CVD was defined as at least one of the following diagnoses (based on the documented medical history): heart failure, coronary artery disease, the history of percutaneous coronary intervention or coronary artery bypass grafting, myocardial infarction, stroke, transient ischemic attack, overt carotid atherosclerosis (understood as the stenosis of at least 50% of diameter), atrial fibrillation and/or peripheral vascular disease.

Statistical Analysis

The data analysis was performed using Microsoft Office Excel and Statistica 13.0 (StatSoft Inc, USA) software . All variables were tested for normality. Continuous variables (such as age, BMI, diabetes duration, HbA1c value etc) were expressed as mean ± standard deviation (SD). As for categorical variables (such as DKD, DR, CVD etc), they were expressed as absolute value and percentage. We compared clinical and demographical data between patients with DPN and without this complication using Student t- test, Chi2 test and regression model analysis. A *P* value below 0.05 was considered statistically significant.

Informed Consent and Bioethics Committee Approval

All subjects gave written, informed consent before being enrolled in the study and the study was performed in accordance with the Declaration of Helsinki and approval by the local Bioethics Committee [ethical approval number PCN/CBN/0022/KB1/104/21]. The study was performed as a part of The Silesia Diabetes-Heart Project registered on ClinicalTrials.gov (NCT05626413).

Results

Two hundred patients were initially considered and 184 ones were finally included into analysis of whom 78 (42%) were men. Figure 1 presents the reasons why 16 patients were not included in the final analysis. Finally, the study population was divided into patients with DPN (69 participants) and without DPN (115 ones) on the basis of MNSI score. In the recruited population the prevalence of DPN was 37.5%. There were 69 subjects diagnosed with DPN in the mean ± SD age of 68.70 ± 11.6 years and 115 participants with MNSI score ≤ 2 in the mean ± SD age of 50.83 ± 17.1 years. Mean BMI was 30.97 ± 6.6 kg/m2 in the group with MNSI score>2 and 28.45 ± 6.1 in the group with MNSI score ≤2. Average duration of diabetes was 15.75 ± 10.8 years in the group with MNSI score>2 and 11.29 ± 9.24 in the group with MNSI score ≤2.

The presence of DKD was identified in 18 (26%) patients with DPN in comparison to 4 (3,5%) patients without this complication. A regression model analysis revealed that the presence of DPN was significantly associated with the presence of DKD (OR = 6.38; 95% CI: 1.86-21.92, $P = 0.0034$;) and patient's age (OR = 1.09; 95% CI: 1.06-1.13, $P < 0.0001$). Thirty-four patients (49.3%) with MNSI score >2 were diagnosed with CVD in comparison to 24 (20.1%) subjects with MNSI score ≤2 ($P = 0.00006$). No significant differences were revealed between 2 study groups with regard to the presence of DR or HbA1c values. Detailed description of the results is presented in Table 1.

Discussion

The key outcomes of our survey suggest a positive association of DPN with the presence of DKD, CVD : BMI and age.

In our cohort, DPN was diagnosed in 37.5% of patients. In general, there are no precise data on DPN prevalence as they differed depending on the type of diabetes, glycemic control, duration of diabetes, age and nation. Moreover, various diagnostic methods are used through the

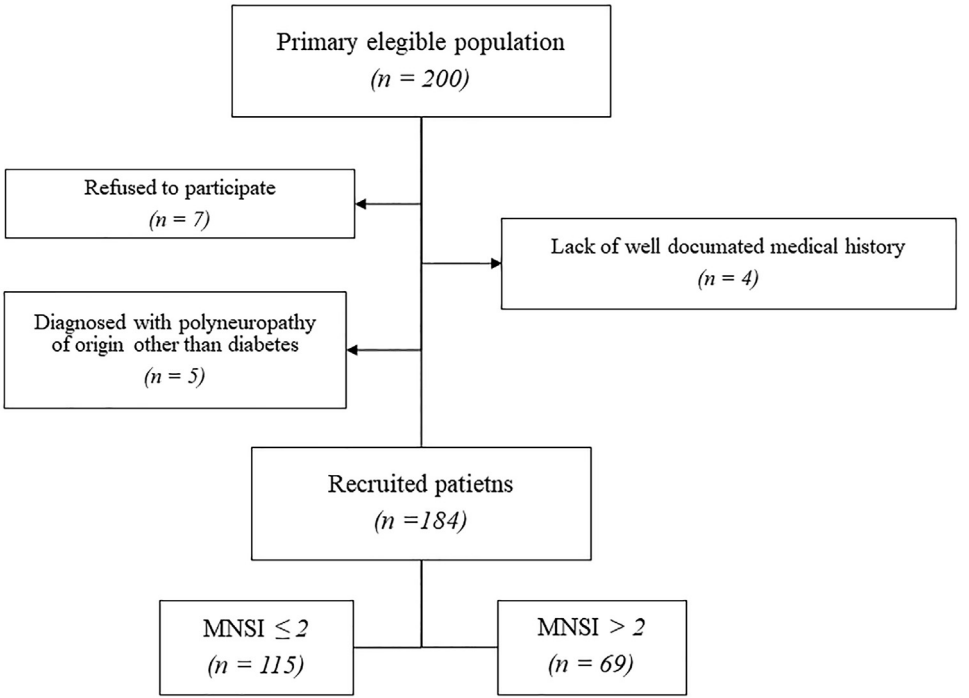

FIG 1. Patients' flowchart. MNSI, The Michigan Neuropathy Screening Instrument.

TABLE 1. Demographic and clinical characteristic of study population

	All Patients (n = 184)	MNSI ≤ 2 (n = 115)	MNSI > 2 (n = 69)	*P* Value (MNSI ≤ 2 vs MNSI > 2)
T1DM, n (%)	54 (29.3)	47 (40.9)	7 (10.1)	0.00001*
T2DM, n (%)	130 (70.7)	68 (59.1)	62 (89.9)	0.00001*
Age (years), mean ± SD	57.53 ± 17.5	50.83 ± 17.1	68.70 ± 11.6	0.00000†
Diabetes duration (years), mean ± SD	12.97 ± 10.1	11.29 ± 9.24	15.75 ± 10.8	0.0034†
Men, n (%)	78 (42.4)	44 (38)	34 39.3	0.1432*
BMI (kg/m^2), mean ± SD	29.4 ± 9.4	28.45 ± 6.1	30.97 ± 6.6	0.0092†
HbA_{1c} (%), mean ± SD	8.7 ± 2.3	8.8 ± 2.4	8.5 ± 2.0	0.4488†
Presence of DR, n (%)	34 (18.5)	17 (14.8)	17 (24.6)	0.095*
Presence of DKD, n (%)	22 (12.0)	4 (3.5)	18 (26)	0.0000*
Presence of CVD, n (%)	58 (31.5)	24 (20.1)	34 (49.3)	0.00006*

*Chi-square test.
†Student t-test.BMI, body mass index; CVD, cardiovascular disease; DKD, diabetic kidney disease; DR, diabetic retinopathy; MNSI, The Michigan Neuropathy Screening Instrument; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

studies therefore their results might differ.[47] During the DCCT/EDIC study 33% participants developed DPN assessed based on the same method of assessment that is, MNSI and our results are comparable with it.[48]

Studies in patients with diabetes show that the association may exist between different microvascular complications, pointing out on the need for search for other complications if one such complication is already diagnosed.[44,49,50] There is a hypothesis of "common soil" suggesting that micro and macrovascular complications of diabetes are closely linked. Brownlee et al.[51] suggested that hyperglycemia causes the overproduction of superoxide which leads to activation of pathways in which tissues are destroyed (ie, polyol, protein kinase C and hexosamine). Following this hypothesis, we have previously performed another trial among T2DM patients with microvascular complications and overt macroangiopathy proving that carotid plaque score is independently associate with microangiopapathic complications of T2DM (ie, retinopathy, DKD and DPN).[57]

Of note, differences in applied methods and criteria for the diagnosis of DPN might have an impact on the results of various research projects. In 2019, a systematic review and meta-analysis assessing the links between different microvascular complications of diabetes indicated no association between DPN and DKD.[53] Out of 26 articles included into meta-analysis only one addressed the possible impact of DPN on DKD.[53]

Concerning the association between DPN and DKD, several studies focused on the association between DPN and DKD in patients with T2DM.[54-56] One showed a strong association between DPN and the prevalence of DKD divided into 4 stages: normoalbuminuria, microalbuminuria, proteinuria, and renal insufficiency.[54] There were 217 patients enrolled in the study and the diagnosis of polyneuropathy was made on the basis of the abnormal results of the electrophysiological assessment.[54] Another study, with similar neuropathy assessment methods, demonstrated that patients who already have DKD (defined as elevated UACR), are at higher risk of developing DPN.[55]

These reports suggest the need of performing screening tests for DPN among patients with T2DM and DKD. One study identified the threshold values of UACR and eGFR which should be considered as potential risk factors for developing DPN. These values were 98.6 mg/dL and 65.3 mL/min/L,73m2 respectively.[49] Patients with T1DM constitute a slightly different group from those with T2DM because of distinct pathogenesis, younger age at the time of diagnosis. Despite insufficient number of studies performed among this group of patients, progression of DKD may be associated with developing DPN.[44]

Nonetheless, the relationship between DKD and DPN may be bidirectional and patients with DPN should be also screened for DKD. Furthermore, cardiovascular autonomic neuropathy, which affects autonomic nerve fibers and may coexists with motor nerve damage, is associated with the presence and progression of DKD.[57,58] In physiological conditions, in order to maintain proper homeostasis, central nervous system and kidney communicate with each other. During pathological states those mechanisms are disrupted and DKD-related mechanisms lead to nervous system damage and vice versa—DPN is a trigger for kidney disease progression.[59] Indeed, microvascular complications, especially DKD, and DR, are associated with higher risk of cardiovascular events,[60-64] especially since mechanisms relevant to atherosclerosis, inflammation and abnormal blood rheology lead to micro- and macrovascular complications, and a higher risk of cardiovascular events with >1 microvascular complication.[37]

The results of another systematic review performed in 2019[65] confirmed reports of previous limited studies[66,67] related to impact of the following risk factors: age, the duration of diabetes, the presence of diabetic DR and higher level of HbA1c on the development of DPN. According to the meta-analysis mentioned above, the duration of diabetes may also have an impact on DPN,[65] as confirmed in our study. When concerning the appearance of the

first potential symptoms of DPN in patients with type 2 diabetes divided into 2 groups, subjects with extended duration of the disease exhibit impaired perception of vibration, prolonged reaction time and balance abnormalities. Patients with less than 5 years of disease duration may achieve worse balance and reaction time tests when compared with nondiabetic subjects.[68]

The results of the mentioned above systematic review performed in 2019 showed no association between BMI and DPN.[65] However, subsequent studies have indicated an increased risk of DPN in the group of patients with a BMI gain of $\geq$1% within a year compared to patients with BMI loss[69] and consistent with the results of our study showing the correlation of the presence of DPN with higher BMI.

When considering the associations between another microvascular complication, namely DR with DPN, the results of performed studies are equivocal. In literature there are reports which confirm the impact of DR on the severity of DPN.[70,71] Peripheral neuropathy is also considered as the risk factor for DR.[72] On the other hand, our study found no association between DR and DPN.[73]

CVD still constitutes the most common cause of death among patients with diabetes.[74] An increased risk of myocardial infarction, CAD, hospitalization for, death from cardiovascular causes and stroke among patients with DPN has been observed.[75,76] This stays in line with the results of our study where the presence of DPN was positively associated with the presence of CVD.

Long-term increase in HbA1c values might be a predictor of the development and progression of DPN, which has been suggested on the basis of real-world data trial performed recently among 1632 T2DM patients observed for 3 years.[77] Contrary, our study showed that there was no association between the HbA1c value and DPN yet we intend to extend our study cohort in the future to verify those findings. However, it's been suggested recently, that data derived from continuous glucose monitoring such as time in range might be a better tool for predicting DPN, especially if in case of patients with more than one complication of diabetes, such as DPN and coexisting DKD.[78]

Although strict management of diabetes can affect the risk of developing complications, intensive glycemic therapy may result in hypoglycemia and escalation of the effects of microvascular comorbidities.[79] Therefore, an individual approach should be applied to each patient. According to American Diabetes Association, the target HbA1c level of 7% ought to be achieved generally, but highly motivated patients with newly-diagnosed diabetes and higher life

expectancy may gain a benefit from more restricted therapeutic goals.[75] There is evidence that rapid decline of HbA1c, especially preceded by a long-term high glucose exposure, may be associated with future cardiovascular events occurrence.[81] This indicates that target glucose levels should be achieved gradually.[80]

Limitations of our study are the relatively small sample size and questionnaire-based DPN assessment. Nevertheless, we aim to expand the research group in order to verify our current findings. The Silesia Diabetes-Heart Project is also designed to be a prospective study with a follow up regarding the occurrence of cardiovascular events among study patients. We also intend to use machine learning techniques for prediction of diabetic complications and we did among patients with metabolic-associated fatty liver disease.[82]

Conclusions

There was an association between DPN and DKD as well as CVD, BMI and age demonstrated. These may indicate that in case of having one diabetes complication diagnosed, it is important to screen for others, including macrovascular ones, as they may be undiagnosed due to their "silent" nature.

Authors' Contribution

Conceptualization, Katarzyna Nabrdalik, Hanna Kwiendacz and Janusz Gumprecht; Data curation, Zenon Brzoza; Formal analysis, Zenon Brzoza; Funding acquisition, Hanna Kwiendacz; Investigation, Justyna Moos and Lukasz Moos; Methodology, Katarzyna Nabrdalik, Hanna Kwiendacz and Janusz Gumprecht; Project administration, Katarzyna Nabrdalik and Hanna Kwiendacz; Resources, Katarzyna Nabrdalik and Hanna Kwiendacz; Supervision, Katarzyna Nabrdalik, Janusz Gumprecht and Gregory Lip; Writing—original draft, Katarzyna Nabrdalik, Hanna Kwiendacz and Justyna Kulpa; Writing – review & editing, Katarzyna Nabrdalik, Hanna Kwiendacz, Tomasz Stompór, Janusz Gumprecht and Gregory Lip. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the local Bioethics Committee [ethical approval number PCN/CBN/0022/KB1/104/21].

Informed Consent Statement

Informed consent was obtained from all subject involved in the study.

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