RESEARCH LETTER

Metabolic control and presence of chronic complications of type 1 diabetes mellitus: 25 years of the Poznan Prospective Study

Aleksandra Cieluch*, Aleksandra Araszkiewicz*, Dariusz Naskręt, Agata Grzelka-Woźniak, Aleksandra Uruska, Dorota Zozulińska-Ziółkiewicz

Department of Internal Medicine and Diabetology, Poznan University of Medical Sciences, Poznań, Poland

Introduction Type 1 diabetes mellitus (T1DM) is an organ-specific autoimmune disease characterized by the destruction of pancreatic islet β cells and absolute insulin deficiency. Epidemiologic data indicate a significant increase in the incidence of T1DM.[1] The DCCT/EDIC (Diabetes Control and Complications Trial / Epidemiology of Diabetes Interventions and Complications) study[2] showed that , in contrast with the conventional treatment method, the use of intensive insulin therapy is associated with lower glycated hemoglobin (HbA_{1c}) concentrations and reduced risk for the development and progression of chronic T1DM complications. Since 1993, intensive insulin therapy has been the gold standard of care in individuals with T1DM and patient education has become an integral part of diabetes treatment. Based on this assumption, the Poznan Prospective Study (PoProStu) was constructed. This was a long-term prospective analysis in which, unlike in the DCCT study (where insulin dose adjustment was performed based on recent blood glucose readings), the participants were treated with intensive functional insulin therapy from the very beginning. All hospitalized patients with newly diagnosed T1DM participated in a 5-day structured training program during which they learned how to administer multiple daily insulin injections and adapt short-acting insulin doses before main meals according to glycemia, carbohydrate content, and planned physical activity.[3]

One of the goals of metabolic control of T1DM is to achieve optimal HbA_{1c} levels while avoiding hypoglycemia. Many patients, both children and adults, especially those with a long-term history of T1DM, do not achieve the target HbA_{1c} values. Proper glycemic control is a chance to avoid short and long-term complications of T1DM.[4,5] Cardiovascular events are the leading cause of death among patients with T1DM,[6] but microvascular complications are a significant cause of blindness, renal failure, amputations, and premature death.[7]

Our study aimed to assess the metabolic control, presence of chronic complications, and mortality in patients with T1DM after 25 years of the disease duration.

Patients and methods **Patients** A total of 71 participants of the PoProStu study (median [interquartile range, IQR] age, 47 [43–51] years) were included in the current analysis. The patients were recruited to the study in the years 1994 to 1998. They remain under constant observation and are regularly assessed for metabolic control and chronic complications.[8] All patients have been treated with intensive insulin therapy. The current analysis concerns the participants with a disease duration of 25 years. Initially, 100 patients were recruited to the study. During the follow-up, 5 individuals died, 9 resigned from participation in the study, and 15 could not be contacted 25 years since the enrollment.[9] At the time of inclusion in the study, all patients signed a consent to participate. The study was approved by the local bioethics committee (823/21). The study is registered on the ClinicalTrials.gov website (NCT01411033).

Anthropometric data, medical history, and laboratory tests The diabetes treatment, presence of complications and comorbidities, use of other medications, and lifestyle behaviors were self-reported using a questionnaire. Weight, height, body mass index (BMI), waist and hip circumferences, and waist-to-hip ratio (WHR) were assessed. BMI (kg/m^2) was calculated using height and weight measurements performed during

Correspondence to:
Aleksandra Cieluch, MD, PhD, Department of Internal Medicine and Diabetology, Poznan University of Medical Sciences, Raszeja Hospital, ul. Mickiewicza 2, 60-834 Poznań, Poland, phone: +48 61 224 52 70, email: aleksandra.cieluch@o2.pl
Received: May 22, 2023.
Revision accepted: July 11, 2023.
Published online: July 14, 2023.
Pol Arch Intern Med. 2023; 133 (7-8): 16534
doi:10.20452/pamw.16534

* AC and AA contributed equally to this work.

outpatient visits. Blood pressure was measured with a sphygmomanometer. Ten milliliters of blood and a morning urine sample were collected from all participants. Laboratory tests were performed on the Cobas 6000 device (Roche Diagnostic, Basel, Switzerland). The level of HbA_{1c} was determined in whole blood by turbidimetry. Serum levels of other parameters were assessed. The enzymatic-colorimetric method was used to determine the concentration of total cholesterol (TC), triglycerides, and high-density lipoprotein cholesterol (HDL-C). The level of low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula.[10] The alanine aminotransferase, aspartate aminotransferase, and γ-glutamyl transpeptidase concentration assessments were performed using the kinetic method (according to the International Federation of Clinical Chemistry). The level of creatinine was determined by the Jaffe method and estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[11] The albumin-to-creatinine ratio was calculated based on the data obtained in direct measurements. The level of C-reactive protein was measured by immunoturbidimetry, and that of thyroid stimulating hormone, by electrochemiluminescence. The daily dose of insulin was defined as the requirement for insulin per kilogram of body weight per day. The degree of accumulation of advanced glycation end-products of proteins in the skin was assessed using the fluorescent properties of the tissue and expressed as the autofluorescence ratio (AGE-Reader, DiagnOptics, Groningen, the Netherlands).[12] The fat tissue content was assessed using the electrical bioimpedance method, with the Body Composition Analyzer Tanita BC-418 MA device (Tanita Corporation, Tokyo, Japan).

Assessment of chronic complications Diabetic retinopathy was diagnosed during an ophthalmologic examination. Fundus examinations were performed using a slit lamp and a Volk lens for indirect ophthalmoscopy. Additionally, the fundus examination in each patient involved fundus photography (2-field 60 degrees) with a TOPCON digital camera (Topcon Corporation, Tokyo, Japan). Diabetic retinopathy was graded according to the American Academy of Ophthalmology classification as no retinopathy, mild nonproliferative, moderate nonproliferative, severe nonproliferative, and proliferative retinopathy.[13]

Diabetic kidney disease was assessed and graded based on preexisting renal impairment, creatinine concentration, eGFR value, and albumin-to-creatinine ratio. The albumin-to-creatinine ratio lower than 30 mg/g in the morning urine sample was considered normal albuminuria or slightly increased albuminuria (A1), while the albumin-to-creatinine ratio of 30 to 300 mg/g was interpreted as moderately increased albuminuria (A2). Overt proteinuria was diagnosed as the albumin-to-creatinine ratio greater than 300 mg/g (A3). The diagnosis of increased urinary albumin excretion was based on 2 positive albumin-to-creatinine ratio results. Diabetic kidney disease was classified into stages based on the result of the eGFR measurement (stage 1, eGFR ≥90 ml/min/1.73 m^2; stage 2, eGFR 60–89 ml/min/1.73 m^2; stage 3, eGFR 30–59 ml/min/1.73 m^2; stage 4, eGFR 15–29 ml/min/1.73 m^2; stage 5, eGFR <15 ml/min/1.73 m^2).

The presence of peripheral neuropathy was assessed based on the medical history and physical examination (sensation of touch with a monofilament weighing 10 g, sensation of vibration with a neurotensiometer and a tuning fork with a vibration scale of 128 Hz, sensation of temperature, sensation of pain with a pin, and knee and ankle reflexes). Diabetic peripheral neuropathy was diagnosed based on the presence of 2 out of 3 of the following clinical findings: clinical symptoms, decreased or absent sensation (touch, vibration, pain, and/or temperature), and/or decreased or absent tendon reflexes.[14]

The diagnosis of cardiac autonomic neuropathy was based on the measurement of heart rate variability using the Cardiosys Extra system (MDE GmbH, Puchheim, Germany). The test consists in assessing heart rate variability under the influence of specific standardized stimuli (deep breathing test, Valsalva test, test in the supine position combined with an orthostatic test, handgrip strength test). Based on the obtained data, the patient was assigned to the group with cardiac autonomic neuropathy when abnormalities were observed in 2 or more heart rate variability tests (confirmed neuropathy). A positive result on the orthostatic test qualified the patient to the group with severe autonomic neuropathy of the cardiovascular system.[15]

Macroangiopathy was assessed based on a history of cardiovascular diseases (ischemic stroke, myocardial infarction, atherosclerosis of the lower limbs, heart failure, cardiovascular death, atherosclerosis of the carotid arteries). The intima-media thickness of the right common carotid artery (cIMT) was determined using the GE Vivid S6 ultrasound device (GE Healthcare, London, United Kingdom) with the 2.4- to 10-MHz linear array probe. All carotid ultrasound examinations were conducted by the same experienced cardiologist-investigator. In the arteries, longitudinal projection images were captured at 16 frames per second for 5 seconds. cIMT of the far wall 1 cm proximally from the bulb was calculated automatically with the Carotid Analyzer for Research (CAD 5) program (Medical Imaging Applications LLC., Coralville, Iowa, United States). The result was the average of 100 automated computed measurements with high accuracy of up to 0.01 mm.

The IMT of 1.5 mm or more indicated the presence of atherosclerotic plaques equivalent to macroangiopathy.[16]

Cardiovascular risk was assessed in the study group according to the European Society of

TABLE 1 Characteristics of the study group (n = 71) 25 years after the diagnosis of type 1 diabetes mellitus

Parameter		Value
Sex	Women	27 (38)
	Men	44 (62)
Duration of diabetes, y		25 (24–26)
Daily dose of insulin, U/kg body weight/day		0.61 (0.5–0.72)
Smoking		18 (25)
Hypertension		34 (48)
Hypothyroidism		14 (20)
Body weight, kg		82 (70.3–94.6)
Fat tissue content, %		24.4 (19.5–31.3)
Fat tissue content above the reference value		33 (46)
BMI, kg/m^2		26.4 (23–30)
Waist circumference, cm		91 (86–105)
Hip circumference, cm		103 (99.5–110)
WHR		0.9 (0.8–1)
HbA_{1c} at the 25-year follow-up, %; mmol/mol		7.9 (7.3–8.6); 63 (56–70)
HbA_{1c} (entire observation period), %; mmol/mol		8.0 (7.2–8.8); 64 (55–73)
HbA_{1c}-SD (entire observation period)		1.41 (1.32–1.52)
HbA_{1c}-CV (entire observation period)		0.18 (0.16–0.19)
CRP, mg/l		1.45 (0.61–2.71)
Total cholesterol, mmol/l; mg/dl		4.97 (4.33–5.38); 192 (167–207.8)
Triglycerides, mmol/l; mg/dl		1.02 (0.78–1.35); 90.5 (68.9–119.5)
LDL-C, mmol/l; mg/dl		2.69 (2.14–3.25); 104 (82.6–125.3)
HDL-C, mmol/l; mg/dl		1.74 (1.42–1.94); 67 (55–75)
Non–HDL-C, mmol/l; mg/dl		3.13 (2.54–3.91); 121 (98–150.8)
ALT, U/l		16 (13–22.8)
AST, U/l		18 (15.3–22)
GGTP, U/l		18 (14–26.3)
TSH, µIU/ml		1.93 (1.38–2.65)
Creatinine, mg/dl		0.88 (0.76–0.99)
eGFR, ml/min/1.73 m^2		97 (84.5–104)
AF ratio, AU		2.6 (2.3–3.03)

Data are presented as median (interquartile range) or number (percentage).

SI conversion factors: to convert ALT, AST, and GGTP to µkat/l, multiply by 0.0167; creatinine to µmol/l, by 88.4.

Abbreviations: AF, autofluorescence; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CRP, C-reactive protein; CV, coefficient of variation, eGFR, estimated glomerular filtration rate; GGTP, γ-glutamyl transpeptidase; HbA_{1c}, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TSH, thyroid-stimulating hormone; WHR, waist-to-hip ratio

Cardiology recommendations.[17] We classified patients as at a very high cardiovascular risk if they had known cardiovascular disease (CVD) or other end-organ damage (proteinuria, renal impairment defined as eGFR <30 ml/min/1.73 m^2, left ventricular hypertrophy, or retinopathy) or the presence of at least 3 major risk factors (age, hypertension, dyslipidemia, smoking, obesity) or T1DM with early onset and long duration (>20 years). High cardiovascular risk was defined as diabetes with a duration of 10 years or more, without end-organ damage, with any other additional risk factor.

Statistical analysis Descriptive statistics were calculated using MedCalc 20.115 (MedCalc Software Ltd., Ostend, Belgium). Compliance of the interval data distribution with the normal distribution was assessed using the Kolmogorov–Smirnov test. Most of the data were not normally distributed. Quantitative continuous data are presented as median with IQR. Categorical variables are presented as the number of cases and percentage.

Results The characteristics of patients 25 years after the diagnosis of T1DM are presented in TABLE 1. At the 25-year follow-up, the median (IQR) HbA_{1c} value was 63 (56–70) mmol/mol (7.9% [7.3%–8.6%]). The percentage of patients with a HbA_{1c} level lower than or equal to 48 mmol/mol (≤6.5%) was 10%, and of those with a HbA_{1c} level lower than or equal to 53 mmol/mol (≤7%) was 18%. The median (IQR) serum level of LDL-C was 2.69 (2.14–3.25) mmol/l; non–HDL-C, 3.13 (2.54–3.91) mmol/l; HDL-C, 1.74 (1.42–1.94) mmol/l; TC, 4.97 (4.33–5.38) mmol/l; and triglycerides, 1.02 (0.78–1.35) mmol/l. A total of 4 participants (6%) reached their LDL-C target. Only 2 participants (3%) met all the criteria of metabolic control in terms of target HbA_{1c}, LDL-C, and blood pressure values. Due to previously diagnosed dyslipidemia, 15 patients (21%) reported taking a statin. The median (IQR) systolic blood pressure was 135 (123.3–147) mm Hg, and the median (IQR) diastolic blood pressure was 82 (77.3–90) mm Hg. Thirty-four patients (48%) had been previously diagnosed with hypertension, and 33 individuals (47%) were treated with angiotensin-converting enzyme inhibitors. There were 18 smokers in the study group (25%). Acetylsalicylic acid was taken by 5 patients (7%). Diabetic retinopathy was diagnosed in 23 individuals (33%) (including 17 cases of nonproliferative and 6 cases of proliferative retinopathy), diabetic kidney disease in 25 (35%) (stage 1, 12 participants [17%]; stage 2, 7 participants [10%]; stage 3, 2 participants [3%]; stage 4, 3 participants [4%]; stage 5, 1 participant [1%]), peripheral neuropathy in 25 (35%), cardiac autonomic neuropathy in 16 (23%) (including 7 cases of severe cardiac autonomic neuropathy), diabetic foot syndrome in 3 (4%), and macroangiopathy in 17 patients (24%) (including 4 cases with myocardial infarction and 2 cases with a history of ischemic stroke). The presence of atherosclerotic plaque in the carotid arteries was found in 13 patients (18%), while the median (IQR) cIMT was 0.74 (0.64–0.85) mm. A total of 25 patients (35%) did not develop any T1DM-related complications. The cardiovascular risk was assessed as high in 18 patients (25%), and very high in 53 individuals (75%).

Discussion Our study showed the metabolic status of the patients and the rate of T1DM complications 25 years after the diagnosis of the disease. We revealed that most patients did not achieve the target LDL-C and HbA_{1c} values, which are important parameters associated with the risk of developing chronic complications.

Bain et al[18] evaluated the outcomes of individuals with T1DM after 50 years of the disease. The patients were treated with various models of insulin therapy (nearly 20% of them used multiple insulin injections). The HbA_{1c} level was similar to that noted in our study, while none of the patients reached the target HbA_{1c} level. The authors reported high levels of HDL-C and TC but did not specify the values of LDL-C or blood pressure. However, fewer patients were treated for hypertension, as compared with our study group, whereas more patients developed severe retinopathy (as many as 43% of the patients underwent laser therapy) and macroangiopathy. A similar proportion of patients developed diabetic kidney disease. The study showed that a long history of T1DM is conducive to a higher incidence of certain complications of the disease.[18]

Our study included more smokers than the DCCT/EDIC cohort after 30 years of intensive insulin therapy (25% vs 11%).[19] Our patients had lower BMI (26.4 vs 29 kg/m^2), higher systolic blood pressure (135 vs 121 mm Hg), and higher diastolic blood pressure (82 vs 70 mm Hg). Fewer patients in our study group were diagnosed with hypertension (48% vs 68%). The levels of LDL-C and HDL-C were similar in both studies (104 vs 98 mg/dl and 67 vs 63 mg/dl, respectively); however, our patients had higher levels of TC (192 vs 177 mg/dl) and triglycerides (90.5 vs 82 mg/dl). The HbA_{1c} levels were similar in both groups (7.9% vs 8%). Our patients were notably less often treated with statins (21% vs 56%), and cardiovascular events were less frequent in our group (8.5% vs 11.5%). In the DCCT/EDIC study cohort, 13% of patients had microalbuminuria and 5% had macroalbuminuria. Comparing the patients included in the PoProStu and DCCT/EDIC studies, it can be concluded that metabolic control, as reflected by HbA_{1c} and LDL-C levels, was not optimal in either group, while the DCCT/EDIC patients were characterized by better blood pressure control.[19]

Nathan et al[20] compared the outcomes of patients after 30 years of T1DM included in the DCCT/EDIC study with the results of their Pittsburgh Epidemiology of Diabetes Complications (EDC) experience. The HbA_{1c} levels in the EDC study were comparable to the HbA_{1c} values of conventionally treated patients included in the DCCT study. This was probably due to the similar method of treatment in both groups of patients. After a few years, there was a decrease in the HbA_{1c} values in EDC patients, which resulted from a change in the treatment method to intensive insulin therapy, similarly to the DCCT study. In the conventional DCCT/EDIC group, the incidence of proliferative retinopathy was 50%, of diabetic kidney disease 25%, and of CVD 14%. Similar results were obtained by the researchers in the EDC study, with 47%, 17%, and 14% of cases of each complication, respectively. In contrast, in the group treated with intensive insulin therapy from the onset of T1DM, the incidence of these complications was significantly lower (21%, 9%, and 9% for proliferative retinopathy, diabetic kidney disease, and CVD, respectively). In the DCCT/EDIC study, 1% of the conventional treatment group and 1% of the intensive treatment group had amputations. In the EDC study, 2% of patients required amputations. In comparison with the above data, the patients included in the PoProStu study had a lower incidence of proliferative retinopathy and CVD, but a higher incidence of diabetic kidney disease.

The main limitation of our study was the inability to assess the parameters of metabolic control and the presence of chronic complications after 25 years of T1DM duration in all patients originally recruited to the PoProStu study. The follow-up assessment took place during the COVID-19 pandemic, which resulted in patients' reluctance to contact health care professionals due to fear of infection. Fifteen patients were lost to follow-up due to the lack of contact. At the same time, given the circumstances, we believe that the number of individuals included in the final analysis was still satisfactory.

In summary, despite the progress in the available treatment of diabetes, 25 years after the diagnosis of T1DM every fifth patient achieved the general goal of glycemic control, few patients met all the criteria of metabolic control, and every third patient experienced chronic complications of the disease. Above all, the results indicate the need to intensify the treatment in patients with long-term diabetes and to identify the factors conducive to the failure of the therapy.

ARTICLE INFORMATION

ACKNOWLEDGMENTS None.

FUNDING The study was supported by a grant from Diabetes Poland (to AC).

CONFLICT OF INTEREST None declared.

HOW TO CITE Cieluch A, Araszkiewicz A, Naskręt D, et al. Metabolic control and presence of chronic complications of type 1 diabetes mellitus: 25 years of the Poznan Prospective Study. Pol Arch Intern Med. 2023; 133: 16534. doi:10.20452/pamw.16534

REFERENCES

1 Mobasseri M, Shirmohammadi M, Amiri T, et al. Prevalence and incidence of type 1 diabetes in the world: a systematic review and meta-analysis. Health Promot Perspect. 2020; 10: 98-115.

2 Nathan DM. Realising the long-term promise of insulin therapy: the DCCT/EDIC study. Diabetologia. 2021; 64: 1049-1058.

3 Araszkiewicz A, Zozulinska-Ziolkiewicz D, Trepinska M, Wierusz-Wysocka B. Knowledge after five-day teaching program in intensive insulin

therapy performed at the onset of type 1 diabetes influence the development of late diabetic complications. Diabetes Res Clin Pract. 2008; 81: 61-67.

4 El Malahi A, Van Elsen M, Charleer S, et al. Relationship between time in range, glycemic variability, HbA_{1c}, and complications in adults with type 1 diabetes mellitus. J Clin Endocrinol Metab. 2022; 107: e570-e581.

5 Hohendorff J, Kwiatkowska M, Pisarczyk-Wiza D, et al. Mutation search within monogenic diabetes genes in Polish patients with long-term type 1 diabetes and preserved kidney function. Pol Arch Intern Med. 2022; 132: 16143.

6 Chiesa ST, Marcovecchio ML. Preventing cardiovascular complications in type 1 diabetes: the need for a lifetime approach. Front Pediatr. 2021; 9: 696499.

7 Bjerg L, Hulman A, Charles M, et al. Clustering of microvascular complications in type 1 diabetes mellitus. J Diabetes Complications. 2018; 32: 393-399.

8 Grzelka-Wozniak A, Uruska A, Szymanska-Garbacz E, et al. Indirect insulin resistance markers are associated with non-alcoholic fatty liver disease in type 1 diabetes. Pol Arch Intern Med. 2023; 5: 16404.

9 Araszkiewicz A, Zozulińska D, Trepińska M, Wierusz-Wysocka B. Is intensive functional insulin therapy the method of choice in newly diagnosed type-1 diabetes mellitus? Pol Merkur Lekarski. 2004; 17: 463-466.

10 Cordova CM, Schneider CR, Juttel ID, Cordova MM. Comparison of LDL-cholesterol direct measurement with the estimate using the Friedewald formula in a sample of 10,664 patients. Arq Bras Cardiol. 2004; 83: 482-487; 476-481.

11 Matsushita K, Mahmoodi BK, Woodward M, et al; Chronic Kidney Disease Prognosis Consortium. Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. JAMA. 2012; 307: 1941-1951.

12 Araszkiewicz A, Naskret D, Niedzwiecki P, et al. Increased accumulation of skin advanced glycation end products is associated with microvascular complications in type 1 diabetes. Diabetes Technol Ther. 2011; 13: 837-842

13 Wilkinson CP, Ferris FL 3rd, Klein RE, et al; Global Diabetic Retinopathy Project Group. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology. 2003; 110: 1677-1682.

14 Araszkiewicz A, Bandurska-Stankiewicz E, Borys S, et al. 2022 Guidelines on the management of patients with diabetes. A position of Diabetes Poland. Curr Top Diabetes. 2022; 2: 1-134.

15 Ewing DJ, Clarke BF. Diagnosis and management of diabetic autonomic neuropathy. Br Med J (Clin Res Ed). 1982; 285: 916-918.

16 Touboul PJ, Hennerici MG, Meairs S, et al. Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011). An update on behalf of the advisory board of the 3rd, 4th and 5th Watching The Risk symposia, at the 13th, 15th and 20th European Stroke Conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011. Cerebrovasc Dis. 2012; 34: 290-296.

17 Cosentino F, Grant PJ, Aboyans V, et al; ESC Scientific Document Group. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020; 41: 255-323.

18 Bain SC, Gill GV, Dyer PH, et al. Characteristics of type 1 diabetes of over 50 years duration (the Golden Years Cohort). Diabet Med. 2003; 20: 808-811.

19 Group DCaCTDEoDIaCESR. Intensive diabetes treatment and cardiovascular outcomes in type 1 diabetes: the DCCT/EDIC study 30-year follow-up. Diabetes Care. 2016; 39: 686-693.

20 Nathan DM, Zinman B, Cleary PA, et al. Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration: the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications and Pittsburgh Epidemiology of Diabetes Complications experience (1983-2005). Arch Intern Med. 2009; 169: 1307-1316.