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# Ophthalmic evaluation in patients after simultaneous pancreas-kidney transplantation (SPK) due to complications of type 1 diabetes mellitus, and in type 1 diabetic patients assessed for eligibility for SPK

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## STRESZCZENIE

**Aim:** Ophthalmic evaluation of patients after simultaneous pancreas-kidney transplantation (SPK) due to complications of type 1 diabetes mellitus, and type 1 diabetic patients assessed for eligibility for SPK.

**Material and methods:** We performed an ophthalmic evaluation in 37 patients after SPK and 49 patients assessed for eligibility for SPK in the Central Clinical Hospital of the Ministry of Interior in Warsaw between January 2016 and March 2020. Ophthalmic evaluation included measurements of best corrected visual acuity, anterior and posterior eye segment examinations, fundus digital photography, and OCT.

**Results:** In the patients after SPK, we found a statistically significant correlation between atrophy in the photoreceptor inner segment/outer segment junction (IS/OS line) on OCT and the pre-transplant HbA1 level. In the group of patients evaluated before and within one year after SPK, we confirmed activation of retinopathy in 66.7% of examined eyes. OCT performed during the assessment of eligibility for SPK revealed atrophy in the IS/OS line in 47% of examined eyes.

**Conclusions:** Changes in the retina associated with poor pre-transplant diabetes control determine the best achievable visual acuity even after long-term normalization of glycemia following SPK. Patients after SPK require frequent comprehensive ophthalmological follow-up examinations during the first year after transplantation because of the risk of diabetic retinopathy progression. Despite the limitations resulting from their baseline status, more than half of all patients after SPK (51%) have a visual acuity of > 0.6 at least in one eye, which is sufficient for independent functioning. Patients eligible for SPK exhibit macular changes on OCT, hypoperfusion on angio-OCT, and 47% atrophy in the IS/OS line.

**KEY WORDS:** diabetic retinopathy, simultaneous pancreas-kidney transplantation, SPK, diabetes mellitus, OCT.

## INTRODUCTION

The number of people diagnosed with diabetes mellitus and diabetic complications is rising steadily. In 2019, approximately 422 million people worldwide had diabetes mellitus [1], of which approximately 351.7 million were people of working age (i.e. 20-64 years old) [2]. In Poland, according to data from the National Health Fund (NFZ) and Statistics Poland (GUS), 2.9 million adults were diagnosed with diabetes in 2018. The figure corresponds to 9.1 per cent of the adult population [3]. Of this number, approximately 5-10% of patients have type 1 diabetes mellitus [4]. Based on the available data, the incidence of type 1 diabetes mellitus has been rising steadily by 2-5% per year [5]. Type 1 diabetes is caused by the destruction of pancreatic β-cells in an autoimmune process induced by triggers (environmental factors) in individuals with a genetic predisposition [6]. Because of young patient age at diagnosis and prolonged duration of the disease, the vast majority of patients with type 1 diabetes mellitus develop complications. Chronic complications can be divided into macroangiopathies (ischemic heart disease, peripheral arterial disease, and stroke), and microangiopathies (retinopathy, nephropathy, and neuropathy).

Diabetic eye disease is a term for several eye conditions associated with diabetes, including diabetic retinopathy and

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diabetic macular edema, but also cataract, glaucoma, double vision, and visual acuity problems arising from changes in lens hydration depending on the degree of glycemia. Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), conducted in the 1980s, showed that 20 years after the diagnosis of diabetes proliferative diabetic retinopathy was present in approximately 50% of patients with type 1 and approximately 25% of patients with type 2 diabetes mellitus [7, 8]. Even though more than 30 years have passed since that study, major advancements have been made in glycemic control and ophthalmic diagnostics, and new therapies for diabetes and ophthalmic conditions have been introduced, diabetic retinopathy still remains the most common cause of blindness among the working-age population in most countries [9].

Diabetic kidney disease (DKD) is characterized by an initial thickening of the glomerular basement membrane and mesangial expansion. The process leads to glomerular and renal hypertrophy, dysregulation of renal hemodynamics, and increased albumin excretion in the urine, followed by progressive diffuse or focal glomerulosclerosis accompanied by tubulointerstitial abnormalities and renal function impairment [10]. The Eurodiab studies based on data collected from European centers showed that microalbuminuria was present in 20.7% and macroalbuminuria in 8.8% of patients with type 1 diabetes mellitus [11].

In Poland, approximately 25% of patients receiving renal replacement therapy have diabetic nephropathy, and the proportion is growing [12]. In the United States, this group accounts for almost 50% of all patients treated with renal replacement therapy [13]. The vast majority are patients with type 2 diabetes. In patients with type 1 diabetes mellitus, the optimal type of renal replacement therapy is pancreas-kidney transplantation from a deceased donor. The most favorable outcomes are believed to be associated with pre-emptive kidney and pancreas transplantation, i.e. carried out in patients who are not yet on dialysis or who have been receiving dialysis treatment for only a short time. Simultaneous pancreas-kidney transplantation with normal graft function improves patient survival by 7-10 years compared with patients undergoing kidney transplantation from a deceased donor [14, 15].

In the group of patients undergoing pancreas transplantation in the Department of Gastroenterological Surgery and Transplantation at the Central Clinical Hospital of the Ministry of Interior and Administration, the overall survival rate is 88% at one year, and 86% at three and five years. The pancreas graft survival rate is 73% at one year, 72% at three years, and 61% at five years, while the kidney graft survival rate is 87%, 83%, and 83% at one, three, and five years after transplantation, respectively [16]. These data look very favorable when compared with the statistics available for diabetic patients undergoing dialysis therapy. In 2004-2008, the five-year survival rate of European diabetic patients on dialysis was approximately 40-41% [17]. In this group of patients, intradialytic hypotension caused by inadequate response of the vascular system to hypovolemia, is especially dangerous [18], as it elevates the risk of cardiac death, and causes myocardial ischemia and arrhythmias. In addition, it increases the hypoperfusion of the already hypoperfused retina, triggering a whole cascade of reactions.

The only method to restore insulin production is transplantation of the pancreas or pancreatic islets. The first pancreas transplant in the treatment of type 1 diabetes mellitus was performed in 1966 [19]. The introduction of cyclosporine and other advanced immunosuppressive agents, combined with advancements in organ preservation techniques and in the diagnosis and treatment of complications, has greatly improved patient outcomes. The currently accepted indications for pancreas transplantation include severe hypoglycemia requiring third-party assistance and medical intervention, without prodromal symptoms or with hypoglycemia unawareness; hyperglycemia complicated by acidosis; labile diabetes associated with large glycemic fluctuations; rapidly progressive diabetic complications (retinopathy, nephropathy, neuropathy) up to moderate stages; and clinical and emotional issues related to insulin therapy. Absolute contraindications to transplantation include active malignancy and infection. There are three types of pancreas transplant procedures: simultaneous pancreas-kidney transplantation (SPK), pancreas transplantation following a successful kidney transplant (PAK, pancreas after kidney), and pancreas-only transplantation (PTA, pancreas transplantation alone). In 1974, pancreatic islet transplantation was performed for the first time, but the outcomes were not satisfactory [20]. The introduction of a less diabetogenic immunosuppressive regimen by the Edmonton team in 2000, together with repeated islet transplants from successive donors, has contributed to improved outcomes. Nonetheless, only 8% of patients did not require insulin therapy five years after transplantation [21], while 90% of patients on insulin therapy had no problems with glycemic control and experienced no episodes of severe hypoglycemia [22].

## AIMS OF THE STUDY

1. Ophthalmic evaluation of patients after simultaneous pancreas-kidney transplantation (SPK) due to complications of type 1 diabetes mellitus.

2. Ophthalmic evaluation of patients undergoing assessment for eligibility for SPK because of complications of type 1 diabetes mellitus.

## MATERIAL AND METHODS

The study was conducted in the Department of Gastroenterological Surgery and Transplantation, and in the Department of Ophthalmology, Central Clinical Hospital of the Ministry of Interior and Administration in Warsaw, between January 2016 and March 2020. The study group consisted of 37 patients after SPK performed because of complications of type 1 diabetes mellitus, and 49 patients with type 1 diabetes assessed for eligibility to undergo the intervention. SPK procedures have been performed in the Department of Gastroenterological

Surgery and Transplantation at the Central Clinical Hospital of the Ministry of Interior and Administration since 2004.

Patients evaluated for eligibility for SPK and pancreas-only transplantation, have been subjected to a comprehensive ophthalmic examination as part of their eligibility assessment protocol at the Department of Ophthalmology, Central Clinical Hospital of the Ministry of Interior and Administration, since 2016. Before that, ophthalmic assessment was frequently carried out at the patients' main care centers. Ophthalmic evaluation includes assessment of distance and near visual acuity based on Snellen charts, slit-lamp anterior segment examination, stereoscopic posterior segment assessment using Volk Digital Wide Field lens, and measurement of intraocular pressure with iCare tonometer. In patients with sufficient transparency of the optical media, we took color photographs of the eye fundus using Canon CX-1 Digital Fundus Camera and performed OCT (Optical Coherence Tomography) scanning of the macula with OptoVue camera or AngioVue camera (for angio-OCT). In addition, the patients completed a questionnaire to provide information about the history of diabetes mellitus and its complications.

The normality of distribution of the continuous variables under study was determined using the Shapiro-Wilk test. Comparisons of the distributions of discrete variables across the groups were performed with the $\chi^2$ test. Differences in the distributions of continuous variables between the two groups were verified by means of the Mann-Whitney test. Comparisons of continuous variables divided into more than two groups were carried out with the ANOVA test (for normally distributed variables) or the Kruskal-Wallis test (for variables with a non-normal distribution). A significance level of 0.05 was applied in all the tests. All statistical calculations were carried out with R 3.6.1 statistical analysis software.

## RESULTS

A total of 37 patients after SPK were examined ophthalmologically based on the protocol outlined above in the Department of Ophthalmology, Central Clinical Hospital of the Ministry of Interior and Administration, between January 2016 and March 2020. The mean age of patients in this group was 38.49 years. The youngest patient at the time of SPK was 23, and the oldest 62 years old. The mean duration of diabetes was 26.58 years (8-40 years), while the mean time since the diagnosis of diabetic retinopathy was nine years (1-30 years). A total of 31 patients (84%) received dialysis treatment before transplantation. In addition, 31 (84%) patients were treated with laser photocoagulation prior to the transplant procedure. Only two did not undergo the treatment, and four were unable to provide an answer to the question. In eight patients (22%), visual acuity was < 0.1 in both eyes, which represents a severe impairment in the ability to perform the activities of daily living. On the other hand, 10 patients (27%) had a visual acuity of ≥ 0.6 in both eyes, and 19 (51%) at least in one eye (Table I).

Since macular OCT imaging requires transparent optical media, performing the examination in patients with advanced diabetes mellitus complicated by diabetic eye disease frequently poses problems. In our group of patients after SPK, OCT could not be performed in six patients in both eyes and in seven patients in one eye. The group included two patients after enucleation: one had lost an eye following a perforating injury, and the other because of complications associated with diabetic eye disease. Another eye was severely atrophied and the patient used an epiprosthesis. Among the patients in whom OCT was done, atrophy in the photoreceptor inner segment/outer segment junction (IS/OS line) was found

**Table I.** Patients after SPK, post-transplant examination

| | All | < 1 year post-Tx | > 1 year post-Tx |
|---|---|---|---|
| Number of Patients | 37 | 20 | 17 |
| Age (years) | | | |
| Mean | 38.49 | 39.1 | 37.76 |
| Min | 23 | 25 | 23 |
| Max | 62 | 62 | 52 |
| Duration of diabetes (years) | | | |
| Mean | 26.58 | 28.53 | 24.5 |
| Min | 8 | 17 | 8 |
| Max | 40 | 40 | 37 |
| Pre-Tx laser therapy | 31 | 19 | 12 |
| Pre-Tx dialysis therapy | 31 | 15 | 16 |
| Visual acuity | | | |
| < 0.1 in both eyes | 8 | 5 | 5 |
| ≥ 0.6 in both eyes | 10 | 7 | 3 |
| ≥ 0.6 in one eye | 9 | 6 | 3 |
| OCT | | | |
| Photoreceptor atrophy | | | |
| in both eyes | 14 | 9 | 5 |
| in one eye | 12 | 6 | 6 |
| Edema | | | |
| in both eyes | 0 | 0 | 0 |
| in one eye | 4 | 4 | 0 |
| Only minor changes | | | |
| in both eyes | 2 | 1 | 1 |
| in one eye | 5 | 4 | 1 |
| Retinopathy grading | | | |
| NPDR | | | |
| in both eyes | 15 | 7 | 8 |
| in one eye | 6 | 5 | 1 |
| PDR | | | |
| in both eyes | 6 | 4 | 2 |
| in one eye | 6 | 5 | 1 |

*Tx – transplantation, OCT – optical coherence tomography, NPDR – non-proliferative diabetic retinopathy, PDR – proliferative diabetic retinopathy*

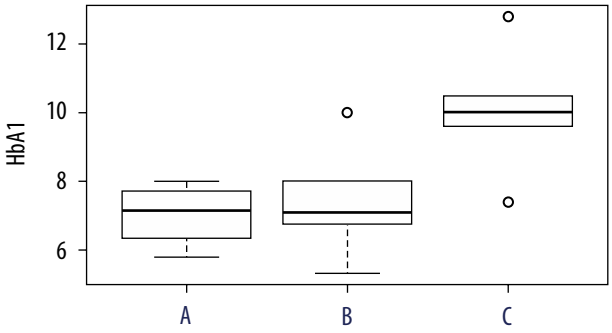


**Figure 1. A)** No signs of athrophy in IS/OS line. **B)** Athrophy in IS/OS line in one eye. **C)** Athrophy in IS/OS line in both eyes

in both eyes in 14 patients and in one eye in 12 patients. Of note, in the eyes where OCT could not be performed because of keratopathy, cataract or vitreous hemorrhages, macular pathologies are also to be expected.

Among the patients who had undergone SPK one year or more previously (17 patients), the OCT findings were close to normal in only one patient in both eyes and in another patient in one eye. These patients were also found to have normal post-transplant creatinine levels.

Analyzing the eyes in which OCT was done (55 eyes), we detected central retinal atrophy in 40 eyes (72 %). Macular

**Table II.** Patients assessed before SPK and after SPK

| | | Vod | Vos | OCT OD | OCT OS | Retinopathy OD | Retinopathy OS | Others |
|---|---|---|---|---|---|---|---|---|
| Patients assessed before SPK | | | | | | | | |
| 1. | BJ | 0.7 | 0.5 | Normal foveal profile, minor atrophy | Foveal profile flattening, atrophy | High-risk PDR | Moderate PDR, NVE in the macular area | No laser therapy |
| 2. | JM | 0.8 | 0.9 | Normal profile, minor atrophy | Normal | Narrow vessels, PRP | Narrow vessels, PRP | Phaco (OD and OS), PPV (OD) |
| 3. | MT | 0.3 | 0,4 | Foveal flattening, atrophy | Foveal flattening, atrophy | Narrow vessels, PRP | Narrow vessels, PRP | Phaco (OD), PPV (OD and OS) |
| 4. | ML | 0.9–1 | 1 | Mild edema, early signs of atrophy | Normal profile, early signs of atrophy | Vessel narrowing, PRP | Vessel narrowing, PRP | |
| 5. | DP | Loss of light perception | Hand movement perception | Keratopathy, no view available | Severe proliferation, detachment | Severe PDR, tractional retinal detachment, PRP | Severe PDR, tractional retinal detachment, PRP | PPV OD oil |
| 6. | DS. | 0.8 | – | DME, ERM, atrophy | No eye | High-risk PDR, membranes in quadrant IV, PRP | No eye | Enucleation (OS), status post-PPV |
| 7. | KK | Hand movement perception | 0.15 | Edema, proliferative membranes, atrophy | ERM, DME, atrophy | PDR, closed vessels, pale optic nerve disc, PRP | PDR, closed vessels, PRP | PPV OD oil |
| 8. | SD | 1 | 0.7 | Normal profile, hypoperfusion | ERM, edema, hypoperfusion | Mild NPDR, vessel narrowing, PRP | Moderate PDR, avascular membranes, PRP | |
| Patients assessed after SPK | | | | | | | | |
| 1. | BJ | 0.7 | 0.5 | Obliterated foveal profile, minor atrophy | Foveal profile flattening, atrophy | High-risk PDR | Moderate PDR, NVE in the macular area, NVD | Rubeosis iridis |
| 2. | JM | 1 | 1 | Minor atrophy | Minor atrophy | Narrow vessels, microaneurysms, PRP | Narrow vessels, microaneurysms, PRP | |
| 3. | MT | 0.3 | 0.2 | Foveal flattening, atrophy | Foveal flattening, atrophy | Narrow vessels, PRP | Narrow vessels, no active changes, PRP | Cataract (OS) |
| 4. | ML | 0.9–1 | 1 | Mild edema, early signs of atrophy | Normal profile, early signs of atrophy | Mild PDR, IRMA, NVE, PRP | Mild PDR, IRMA, NVE, PRP | |
| 5. | DP | Loss of light perception | Hand movement perception | No view | Detachment | Detachment | Detachment | PPV (OS) oil |
| 6. | DS. | 0.9 | – | Atrophy, ERM, traction | No eye | PDR, avascular proliferative membranes in quadrant IV, PRP | No eye | |
| 7. | KK | Uncertain light perception | 0.01 | No view | Atrophy, pseudo macular hole, DME | No view | Closed vessels, pale disc | Mature cataract (OD) |
| 8. | SD | 0.8 | 0.6 | Shallow fovea, atrophy | Shallow fovea, atrophy | NPDR, ERM, isolated hemorrhages, PRP | Avascular proliferative membranes quandrant III, PRP | |

*DME – diabetic macular edema; ERM –epiretinal membrane; IRMA – intraretinal microvascular abnormality; NPDR – non-proliferative diabetic retinopathy; OCT – optical coherence tomography; PDR – proliferative diabetic retinopathy; PPV – pars plana vitrectomy; PRP – panretinal photocoagulation; SPK – simultaneous pancreas-kidney transplantation*

edema due to epiretinal membranes was noted in four eyes (7%).

In the group of patients after SPK, we identified a statistically significant relationship between atrophy developing in the photoreceptor line and in the RPE line, as seen on post-transplant macular OCT, and the level of HbA1 determined in the patients' pre-transplant evaluation. The relationship was checked with the ANOVA test. In patients with atrophy of the photoreceptor inner/outer segment junction (IS/OS line), the mean pre-transplant HbA1 level was 10.06% (±1.936). However, in the group of patients with atrophy in the IS/OS line in one eye the mean pre-transplant HbA1 level was 7.41 ±1.469, and in the group without signs of atrophy in the IS/OS line on structural OCT scans it was 7.02 ±0.932 (Figure 1).

In our study group of patients after SPK, normal HbA1 results were noted both in patients in their first post-transplant year and patients one or more years after the transplantation. The HbA1 level was > 7.0% in just two patients (one in the group < 1 year after SPK and one in the group ≥ 1 year after SPK).

We analyzed the status of diabetic retinopathy in all patients after SPK, taking account of the limitations outlined above. We found non-proliferative diabetic retinopathy (NPDR) in both eyes in 15 patients (40.5%) and in one eye in six patients (16%). Proliferative retinopathy was present in 12 patients (32%): in six patients in both eyes and in another 6 patients in one eye (16%) (Table I).

We examined a total of 71 eyes. Full panretinal photocoagulation had been performed in 46 eyes, and partial laser therapy in 14 eyes. Only one patient (eight years after SPK) had not undergone laser therapy. The patient was diagnosed with mild non-proliferative retinopathy in both eyes, with only isolated microaneurysms.

In the group of patients after SPK, a total of 17 individuals (46%) had undergone cataract surgery, including 13 (35%) with both eyes operated on. Cataract was present in 11 (30%) patients, with binocular cataract detected in six of them (16%).

A total of eight patients (15 eyes) were subjected to an ophthalmic examination according to the protocol outlined above before and up to 12 months after the transplantation (Table II). One patient in the study group was monocular following enucleation of the other eye due to secondary glaucoma that developed after vitrectomy with silicone oil endotamponade performed to treat advanced diabetic retinopathy. We noted an improvement in vision in three eyes (20%), stabilization in seven eyes (47%), and deterioration in five eyes (33%). In this group, seven patients (87.5%) had undergone panretinal photocoagulation (13 eyes). Despite laser therapy, three eyes exhibited changes consistent with active retinopathy, including microaneurysms, IRMA, and active neovascularization (densely branching neovascular network with preserved blood flow). The patient who had not undergone retinal laser therapy had active changes in both eyes. He had been referred for laser therapy to a center in his place of residence (because of considerable travel distance), but the procedure had not been performed before the transplant. The post-transplant examination revealed active changes in 10 eyes (66.7%). In the patient who had not undergone laser

**Table III.** Patients assessed for eligibility for SPK

| | |
|---|---|
| Number of patients | 49 |
| Age (years) | 38.73l (26-60) |
| Duration of diabetes (years) | 26.04l (5-54) |
| Pre-Tx laser therapy | 41 |
| Pre-Tx dialysis therapy | |
| hemodialysis | 32 |
| peritoneal dialysis | 4 |
| Visual acuity | |
| < 0.1 in both eyes | 2 |
| ≥ 0.6 in both eyes | 17 |
| ≥ 0.6 in both eyes | 15 |
| OCT | |
| Photoreceptor atrophy | |
| in both eyes | 11 |
| in one eye | 19 |
| DME | |
| in both eyes | 2 |
| in one eye | 11 |
| Only minor changes | |
| in both eyes | 13 |
| in one eye | 10 |
| Retinopathy grading | |
| No signs of retinopathy | 1 |
| NPDR in both eyes | 18 |
| in one eye | 6 |
| PDR in both eyes | 22 |
| in one eye | 10 |
| High-risk PDR | |
| in both eyes | 9 |
| in one eye | 7 |
| PC lens | |
| in both eyes | 3 |
| in one eye | 10 |
| Own lens | |
| clear in both eyes | 13 |
| in one eye | 12 |
| cataract in both eyes | 5 |
| in one eye | 9 |

*SPK – simultaneous pancreas-kidney transplantation; DME – diabetic macular edema; Tx – transplantation, OCT – optical coherence tomography, NPDR – non-proliferative diabetic retinopathy, PDR – proliferative diabetic retinopathy*

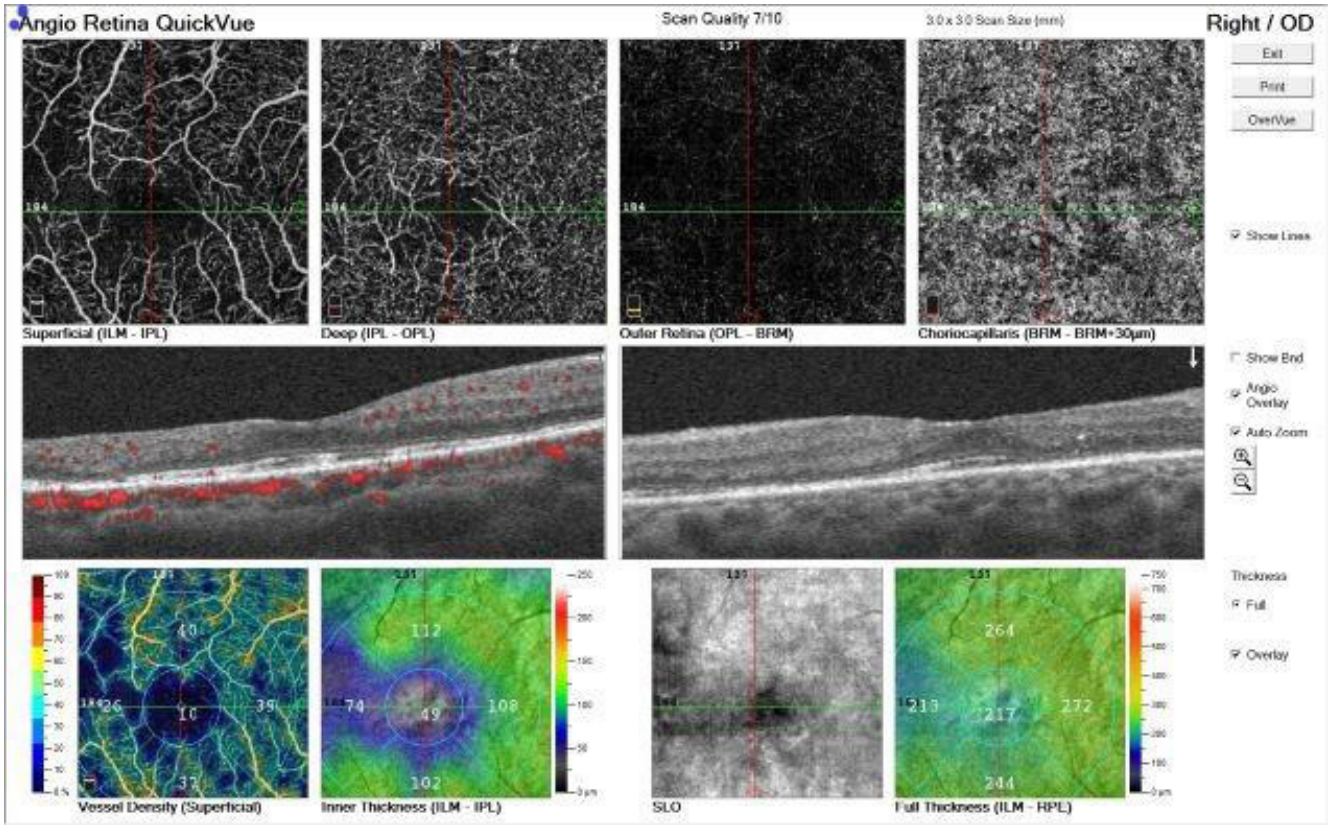


**Figure 2.** OCT A of a patient assessed for eligibility for SPK. Deficiencies in superficial and deep capillary plexuses, enlargment of the foveal avascular zone (FAZ)

therapy, visual acuity and retinopathy grade (moderate PDR) remained stable, but an increase in the number of active lesions was observed.

Among the patients assessed in our center before and after SPK, we were able to perform pre-transplant OCT in 13 eyes. Varying degrees of atrophy in the photoreceptor line were found in as many as 10 of them (77%). In only two eyes evaluated as part of the pre-transplant examination the structural OCT findings were close to normal, while the eye where angio-OCT was performed showed signs of hypoperfusion. After the transplantation, both eyes exhibited atrophy in the IS/OS line. Post-transplant OCT examination was possible in 12 eyes, with atrophy in the IS/OS line found in all of them (100%).

As part of eligibility assessment for pancreas-kidney transplant, we evaluated a total of 49 patients with type 1 diabetes mellitus. The mean age of the patients was 38.73 years (Table III), and the mean time since the diagnosis of diabetes was 26.04 years. During the assessment of eligibility, 36 patients (73%) were on dialysis. The majority (32 patients, 65%) received regular hemodialysis and four patients (8%) were treated with peritoneal dialysis. A total of 41 patients (84%) in this group had previously undergone retinal laser therapy. Of the total group, one patient had no visible signs of diabetic retinopathy in the stereoscopic fundus examination. This was a patient with type 1 diabetes mellitus and agenesis of the left kidney, in whom failure of the sole kidney had not occurred as a result of diabetic nephropathy. However, we found proliferative diabetic retinopathy in 32 patients (65%), including 22 patients (45%) with both eyes affected. Nine patients (18%) had high-risk proliferative retinopathy in both eyes and seven (14%) in one eye. Visual acuity of 0.6 or better in both eyes was noted in 17 (35%) patients and in one eye in 15 (31%) patients. Only two (4%) patients had a visual acuity of < 0.1 in both eyes. A total of 13 (26%) patients had previously undergone cataract surgery, of whom three had artificial lenses in both eyes. Only 13 (26%) patients had a clear lens in both eyes. Cataract was present in 14 (28%) patients, including binocular cataract in five (10%) individuals. OCT was carried out in 85 eyes, with atrophy in the IS/OS line identified in 40 eyes (47%). In 15 eyes (18%), the macular findings seen on structural OCT were close to normal, while in the eyes in which angio-OCT could be performed we found evidence for macular hypoperfusion.

## DISCUSSION

Our study, conducted in a group of patients after SPK, revealed a statistically significant relationship between the development of atrophy in the photoreceptor inner segment/outer segment junction (IS/OS line), as seen on macular OCT, and the level of HbA1 determined in the patients' pre-transplant evaluation. This correlation provides evidence for the importance of successful glycemic control in inhibiting the development of diabetic retinopathy. Recurrent episodes of hyperglyce-

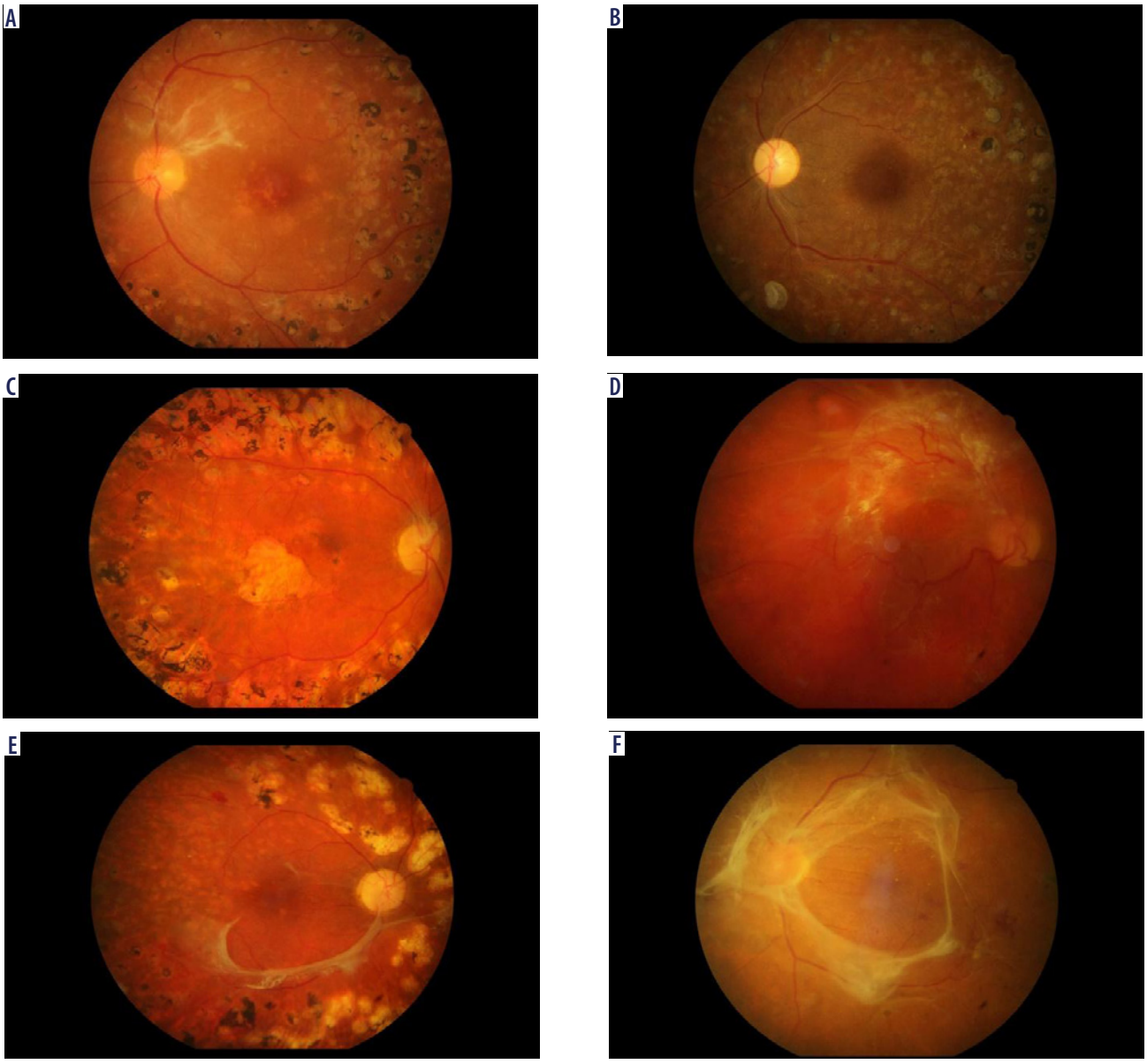


**Figure 3.** Sample photos of patients assessed for eligibility for SPK. **A)** Proliferative membranes on optic disc; narrow arteries partially ocluded, maculopathy, panretinal photocoagualtion. **B)** Narrow arteries partially ocluded, panretinal photocoagualtion, spots also inside of vascular arcade. **C)** Scar in the macular area. **D)** Vascularized proliferative membranes along the arcades obscuring macular area. **E)** Avascular proliferative membranes along the lower arcade and macular area. **F)** Proliferative membranes on optic disc, along the vascular arcades, and temporaly from the macula with multiple tractions, ERM creating folds on retinal surface

mia over the course of many years cause permanent damage to the retina. Hyperglycemia activates the polyol pathway, leading to the accumulation of sorbitol which, in turn, induces osmotic stress, decreased activity of the sodium-potassium pump, and depletion of other antioxidant mechanisms. These processes have a crucial impact on the condition of the retina which, as a neurovascular tissue (composed of 5% blood vessels and 95% neurons and glial cells [23]), is highly sensitive to oxidative stress [24, 25]. Hyperglycemia also induces the synthesis of growth factors, neuronal apoptosis, accumulation of AGEs (advanced glycation end-products), and activation of protein kinase C. This results in permanent neuronal damage, loss of pericytes, uncontrolled endothelial growth, and thickening of the basement membrane [26]. It needs to be highlighted that these pathologies develop before any changes can be seen in the fundus of the eye.

Pancreas transplantation leads to the normalization of glycemia and HbA1C levels without the need for insulin therapy, and helps avoid the risk of hypoglycemia [27]. The transplanted pancreas retains the pulsatile nature of insulin release. Glucagon secretion in response to hypoglycemia is also restored [28]. The return of insulin production has a beneficial effect on autonomic neuropathy, which is manifested by improved hormonal response to hypoglycemia, normalized heart rate variability, gastric emptying time, and better skin temperature regulation [29]. Other observed benefits include improved lipid metabolism, reduced triglyceride and LDL cholesterol levels, and elevated HDL levels.

The prevailing view is that pancreas transplantation has benefits for the treatment of diabetic retinopathy on the condition that it is performed early. Studies conducted on rats with induced diabetes mellitus showed that pericytes and endothelial cells in retinal capillaries became damaged at an early disease stage. Improvement in the condition of the capillaries within the superficial and deep capillary networks and reduced incidence of cataract were observed only in the rats that received the transplant early (i.e. two weeks after diabetes induction). In the late transplant group (performed 12 weeks after the induction of diabetes), no improvement in vascular condition or decrease in cataract incidence was observed [30].

The results of our study are consistent with these findings. In the post-SPK group, as many as 72% of patients were found to have central retinal atrophy, and 14% – diabetic macular edema. It may be assumed that the vast majority of eyes that were not amenable to assessment because of the loss of transparency of the optical media also show a significant degree of damage in the posterior pole, and the photoreceptors were already damaged prior to the transplant procedure.

In the group of patients assessed for eligibility for SPK, atrophy in the photoreceptor line seen on structural OCT was found in 47% of eyes. Only in 18% of eyes the macular findings on structural OCT were close to normal. In diabetic patients, when structural OCT reveals a normal macular appearance and stereoscopic examination shows no abnormalities in the eye fundus, angio-OCT commonly reveals macular hypoperfusion. Angio-OCT is a highly sensitive method for detecting early retinal changes associated with diabetic retinopathy (Figure 2). Retinal vascular damage induced by diabetes is relatively well understood. Nevertheless, considerably less is known about the pathomechanism underlying retinal neuronal damage: ganglion cell atrophy and degeneration in the inner nuclear layer which are characterized by a very early onset and precede vascular changes [31–33]. In cases where macular changes are significant, the normalization of glycemia, blood pressure and lipid metabolism does not contribute to improving vision (Figure 3). Despite all these limitations, more than half of all patients (51%) had a visual acuity of ≥ 0.6, which allows independent functioning, at least in one eye. Visual acuity values of < 0.1 in both eyes were obtained in 22%.

In the group of patients assessed in our center before and during the first year after SPK (8 patients), improved vision was noted in 20%, stable vision in 47%, and deteriorated vision in 33% of eyes. Unfortunately, because of factors including the need to travel long distances from their homes to our center and, in many cases, mobility difficulties related to the patients' general health status and life situation, this was a small group. Among these patients, signs of active diabetic retinopathy were detected in 33% and 67% of the eyes before and after SPK, respectively. This observation is consistent with the findings of the Diabetes Control and Complications Trial (DCCT). The study showed that a decrease in HbA1 to normal levels during the first year elevated the risk of retinopathy progression, and it was not until three years after the commencement of strict glycemic control that a 54% reduction in the risk of significant progression of retinopathy was noted [34]. The conclusion of the DCCT study is that close ophthalmic monitoring is required during the intensification of diabetes treatment [35]. The findings of our study are consistent with this conclusion. After SPK, patients attain very good glycemic control. During the first post-transplant year, an increase in the number of active changes associated with diabetic retinopathy is observed, which is why close ophthalmic monitoring is necessary and supplementary photocoagulation should be performed where necessary. To reduce the risk of progression of diabetic retinopathy after pancreas transplantation, it is advisable to stabilize the patient's retina in preparation for the transplant procedure through photocoagulation and/or anti-VEGF therapy.

The results of studies evaluating the effects of pancreas transplantation on the status of diabetic retinopathy are inconclusive, and benefits are usually seen after a longer follow-up. A study comparing the outcomes of patients after SPK in whom pancreatic graft function was normal (22 patients) with patients in whom the pancreas transplant failed (16) revealed no differences in retinopathy progression during the first two years of follow-up [36]. Ramsay *et al*. concluded that a successful pancreas transplant and the resulting normoglycemia neither reverses the damage associated with diabetic retinopathy nor prevents its progression. In contrast, Ulbig *et al*., in a study with longer patient follow-up (mean > 3 years, up to 6 years), observed vision improvement in 32% of patients, stabilization in 46%, and deterioration in 22% [37]. In their comparison of a group of 30 patients after SPK with a control group of 15 patients after SPK and pancreatic graft rejection, Kőnigsrainer *et al*. observed stabilization of retinopathy in 73%, improvement in 8.8%, and deterioration in 17.7% of eyes in patients after successful pancreas and kidney transplantation. The authors concluded that a successful pancreas transplant had a beneficial effect on the treatment of diabetic retinopathy [38]. The positive impact of successful pancreas transplantation on the stabilization or improvement of diabetic retinopathy was also reported by other authors [39–41].

To produce an improvement in vision, the transplantation procedure must be carried out before the onset of irreversible damage in the retina. Currently, the majority of transplant procedures are performed in patients with end-stage renal disease, who usually present with very advanced diabetic retinopathy. It needs to be highlighted that the primary changes underlying retinopathy – neuronal damage and pathological capillary remodeling – occur before the first microaneurysms can be identified. Deteriorating kidney function (rise in creatinine level, loss of albumins, increasing endothelial cell dysfunction, growing oxidative stress) accelerates the cascade of damage in the retinal neurons and the capillary network. Diabetes is associated with simultaneous disorders in the deep retinal capillary network (visible on angio-OCT) and disruption in the choroidal circulation due to impairment in autoregulation mechanisms, which leads to increasing oxygen deficit of photoreceptors and their progressive damage [42].

Most patients undergo panretinal photocoagulation before transplantation. The procedure is often very intensive and covers the area within the arcades. The Diabetic Retinopathy Study showed that appropriate and timely laser therapy reduced the risk of severe vision loss by at least 50% in patients with proliferative diabetic retinopathy [43]. Nonetheless, it is also important to bear in mind the negative effects of panretinal photocoagulation such as increasing macular edema [44, 45], significant decrease in the peripheral visual field, impairment of color vision [46, 47] and night vision [48], and reduced contrast sensitivity. Many patients scheduled for transplantation already have a history of cataract surgery and/or vitrectomy. The degree of achievable improvement is strongly limited by previous significant and largely irreversible damage to the eye.

## SUMMARY

It has been debated for years whether successful pancreas-kidney transplantation improves or stabilizes the organ of vision. Based on the findings of our study, it can be concluded that the baseline status of patients has a key impact on the treatment outcomes that can be achieved. In the group of patients after SPK, we found a statistically significant relationship between the development of atrophy in the photoreceptor inner segment/outer segment junction (IS/OS line) on macular OCT after the transplant and the level of HbA1 determined in the patients' pre-transplant evaluation. Furthermore, in the group of patients assessed for eligibility for SPK, we detected atrophy in the IS/OS line in 47% of eyes on structural OCT, while in the eyes that showed no changes on structural OCT, there was expansion of the avascular zone and capillary atrophy within the deep retinal capillary plexus.

Despite these limitations, more than half (51%) of the patients after SPK have a visual acuity of > 0.6 at least in one eye, which is sufficient for independent functioning, and 27% in both eyes. Poor visual acuity (< 0.1) in both eyes, which severely impairs the ability to perform the activities of daily living, was found in 22% of patients after SPK.

## CONCLUSIONS

1. The level of HbA1 before simultaneous pancreas-kidney transplantation is correlated with post-transplant damage in the IS/OS line seen on OCT. Retinal alterations due to poor diabetes control before transplantation determine the extent of improvement in visual acuity that can be achieved in patients even after long-term post-transplant normalization of glycemia.

2. Patients after SPK require frequent and comprehensive ophthalmological follow-up examinations during the first post-transplant year because of the risk of retinopathy progression. To reduce the risk of progression of diabetic retinopathy after pancreas transplantation, it is advisable to stabilize the retina in preparation for the transplant procedure via photocoagulation and/or anti-VEGF therapy.

3. Despite the limitations resulting from their baseline status, more than half of all patients after SPK (51%) have a visual acuity of > 0.6 at least in one eye, which is sufficient for independent functioning.

4. In addition to diabetic nephropathy, patients assessed for eligibility for SPK have diabetic retinopathy, macular OCT changes (hypoperfusion visible on angio-OCT scans). Almost half of them have atrophy in the IS/OS line.

## DISCLOSURE

The authors declare no conflict of interest.

### References


1. World Health Organization. Available at: https://www.who.int/health-topics/diabetes#tab=tab_1 (Access: 20.07.2020).
2. International Diabetes Federation. IDF Diabetes Atlas. Ninth edition 2019. Available at: https://www.diabetesatlas.org/upload/resources/material/20200302_133351_IDFATLAS9e-final-web.pdf (Access: 20.07.2020).
3. Narodowy Fundusz Zdrowia o zdrowiu. Cukrzyca. Available at: https://zdrowedane.nfz.gov.pl/pluginfile.php/205/mod_resource/content/4/nfz_o_zdrowiu_cukrzyca.pdf (Access: 20.07.2020).
4. Levy D. Praktyczna opieka diabetologiczna. Wyd. Lek. PZWL, Warszawa 2013: 7-31.
5. Dhaliwal R, Weinstock R. Management of Type 1 Diabetes in Older Adults. Diabetes Spectr. 2014; 27: 9-20.
6. Sieradzki J. Płaczkiewicz-Jankowska E. Zaburzenia gospodarki węglowodanowej. W: Gajewski P (red.). Interna Szczeklika 2019/20. Medycyna Praktyczna, Krakow 2020: 876.
7. Klein R, Klein BE, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. II. Prevelence and risk of diabetic retinopathy when age of diagnosis is less than 30 years. Arch Ophtalmol 1984; 102: 520-526.
8. Klein R, Klein BE, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. III. Prevelence and risk of diabetic retinopathy when age of diagnosis is 30 or more years. Arch Ophtalmol 1984; 102: 527-532.
9. International Diabetes Federation. IDF Diabetes Atlas. Ninth edition 2019: 36. https://www.diabetesatlas.org/upload/resources/material/20200302_133351_IDFATLAS9e-final-web.pdf (Access: 20.07.2020 r.).
10. Czekalski S. Nefropatia cukrzycowa. In: Książek A, Rutkowski B (ed.). Nefrologia. Wydawnictwo Czelej, Lublin 2004: 346-371.
11. EURODIAB Complications Study Group. Microvascular and acute complications in IDDM patients: the EURODIAB IDDM Complications Study. Diabetologia 1994; 37: 278–285.
12. Rutkowski B. Epidemiologia chorob nerek w populacji chorych na cukrzycę. In: Franek E, Grzeszczak W, Kokot F (red.). Nefrodiabetologia. Wydawnictwo Via Medica, Gdańsk 2015.
13. United States Renal Data System: 2012, USRDS 2014, Annual Data Report; Atlas of end-stage renal disease in the United States. National Institutes of Diabetic and Digestive and Kidney Disease. Bethesda 2010.
14. Larsen L. Pancreas Transplantation: Indications and Cosequences. Endocrine Reviews 2004; 25: 919-946.

15. Venstrom JM, McBride MA, Rother KI, et al. Survival after pancreas transplantation in patients with diabetes and preserved kidney function. JAMA 2003; 290: 2817-2823.
16. Durlik M, Baumgart K. Przeszczepienie trzustki oraz izolowanych wysp trzustkowych w leczeniu cukrzycy. W: Franek E, Grzeszczak W, Kokot F (red.). Nefrodiabetologia. Wyd. III. Wydawnictwo Via Medica, Gdańsk 2015.
17. Kramer A, Pippias M, Stel V, et al. Renal replacement therapy in Europe: a summary of the 2013 ERA-EDTA Registry Annual Report with a focus on diabetes mellitus. Clin Kidney J 2016; 9: 457-469.
18. Kopeć J, Sułowicz W. Leczenie nerkozastępcze w nefropatii cukrzycowej. Diabetol Prak 2003; 4: 21-25.
19. Kelly WD, Lillehei RC, Merkel FK, et al. Allotramsplantation of the pancreas and duodenum along with the kidney in diabetic in diabetic nephropathy. Surgery 1967; 61: 827-837.
20. Najarian JS, Sutherland DE, Matas AJ, et al. Human islet transplantation: a preliminary report. Transplant Proc 1977; 9: 233-236.
21. Ryan EA, Paty BW, Senior PA, et al. Five-year follow-up after clinical islet transplantation. Diabetes 2005; 54: 2060-2069.
22. Gołębiewska J, Witkowski P, Dębska-Ślizień A. Przeszczepienie wysp trzustkowych. Forum Nefrol 2018; 11: 24-32.
23. Bughi S, Bessman A, Shaw S. Understanding diabetic retinopathy and its visual implications. W: Boyd S, Girah A, Pelayes DE. Diagnostic and Treatment of Diabetic Retinopathy Jaypee – Highlights Medical Publishers, INC 2010: 1-20.
24. Balasubbramanyan M, Rema M, Premanand C. Biochemical and molecular mechanism of diabetic retinopathy and diabetic macular edema disease severity scales. Curr Sci 2002; 83: 1506-1514.
25. Karpińska A, Gromadzka G. Stres oksydacyjny i naturalne mechanizmy antyoksydacyjne – znaczenie w procesie neurodegeneracji. Od mechanizmow molekularnych do strategii terapeutycznych. Postepy Hig Med Dosw 2013; 67: 45-53.
26. Ryan EA, Bigam D, Shapiro AM. Current indications for pancreas or islet transplant. Diabetes Obes Metab 2006; 8: 1-7.
27. Milczarczyk A, Durlik M, Franek E. Przeszczepienie trzustki i wysp trzustkowych w leczeniu cukrzycy typu 1. Post N Med 2007; 5: 165-167.
28. Spadella CT, Machado JLM, Lerco MM, et al. Temporal relationship between succesful pancreas transplantation and control of ocular complications in alloxan-induced diabetic rats. Transplant Proc 2008; 40: 518-523.
29. Barber AJ, Lieth E, Khin SA, et al. Neural apoptosis in the retina during experimental and human diabetes. Early onset and effect of insulin. J Clin Invest 1998; 102: 783-791.
30. Verma A, Rani PK, Raman R, et al. Is neuronal dysfunction an early sign of diabetic retinopathy? Microperimetry and spectra domain optical coherence tomography (SD-OCT) Study in individuals with diabetes, but not diabetic retinopathy. Eye 2009; 23: 1824-1830.
31. Ng DS, Chiang PP, Tan G, et al. Retinal ganglion cell neuronal damage in diabetes and diabetic retinopathy. Clin Exp Ophtalmol 2016; 44: 243-250.
32. Diabetes Control and Complications Trial Research Group; Nathan DM, Genuth S, Lachin J, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329: 977-986.
33. Santiago JV. Lessons from the Diabetes Control and Complications Trial. Diabetes 1993; 42: 1549-1554.
34. Ramsay RC, Goetz FC, Sutherland DE, et al. Progression of diabetic retinopathy after pancreas transplantation for insulin-dependent diabetes mellitus. N Enl J Med 1988; 318: 208-214.
35. Ulbig M, Kampik A, Thurau S, et al. Long-term follow-up of diabetic retinopathy for up to 71 months of diabetic retinopathy for up to 71 months aftercombined renal and pancreatic transplantation. Graefes Arch Clin Exp Ophtalmol 1991; 229: 242-245.
36. Konigsrainer A, Miller K, Steurer W, et al. Does pancreas transplantation influence the course of diabetic retinopathy? Diabetologia 1991; 34 Suppl 1: S86-88.
37. Giannarelli R, Coppelli A, Sartini M, et al. Effects of pancreas-kidney transplantation on diabetic retinopathy. Transpl Int 2005; 18: 619-622.
38. Koznarowa R, Saudek F, Sosna T, et al. Beneficial effect of pancreas and kidney transplantation on advanced diabetic retinopathy. Cell Transplant 2000; 9: 903-908.
39. Pearce IA, Ilango B, Sells R, Wong D. Stabilisation of diabetic retinopathy following simultaneous pancreas and kidney transplant. Br J Ophtalmol 2000; 84: 736-740.
40. Scarinci F, Nesper P, Fawzi A. Deep retinal capillary nonperfusion is associated with photoreceptor disruption in diabetic macular ischemia. Am J Optalmol 2016; 168: 129-138.
41. Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy. Clinical application of Diabetic Retinopathy Study (DRS) findings, DRS Report Number 8. Ophtalmology 1981; 88: 583-600.
42. McDonald HR, Schatz H. Visual loss following panretinal photocoagulation for proliferative diabetic retinopathy. Ophtalmology 1985; 92: 388-393.
43. Diabetic Retinopathy Clinical Research Network; Brucher AJ, Qin H, Antoszyk AN, et al. Observational study of the development of diabetic macular edema following panretinal (scatter) photocoagulation given in 1 or 4 sittings. Arch Ophtalmol 2009; 127: 132-140.
44. Russel PW, Sekuler R, Fetkenhour C. Visual function after pan-retinal photocoagulation: a survey. Diabetes Care 1985; 8: 57-63.
45. Early Treatment Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. Ophtalmology 1991; 98: 766-785.
46. Fong DS, Girach A, Boney A. Visual side effects of successful scatter laser photocoagulation for proliferative diabetic retinopathy: a literature review. Retina 2007; 27: 816-824.