

HEMOPERFUSION AND FUNCTIONAL STATE OF THE MACULA AFTER SIMULTANEOUS PANCREAS AND KIDNEY TRANSPLANTATION

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Simultaneous pancreas and kidney transplantation (SPK) provides effective treatment in patients with type 1 diabetes mellitus (T1DM) and end-stage renal failure (ESRF), mitigating the hyperglycemia and uremic syndrome. The study aimed at the assessment of morphofunctional status of the macula and macular hemodynamics in patients with T1DM after SPK. The study enrolled 45 patients subdivided into three groups: Group A — patients with T1DM after SPK; Group B — patients with T1DM and ESRF, maintained on programmed hemodialysis (PH), on waiting list for SPK; and Group C — individuals without ophthalmic or systemic pathologies. All patients were subject to the standard ophthalmological examination complemented by measurements of the central retinal thickness (CRT) and the average perfusion density (PD) in four vascular layers: superficial capillary plexus of the retina (SCP), deep capillary plexus of the retina (DCP), choriocapillaris, and choroid. The patients after SPK had significantly lower CRT ($241 \pm 33 \mu\text{m}$ in Group A, $309 \pm 10 \mu\text{m}$ in Group B; $p < 0.05$) and significantly higher PD of the macular region in both the retina (Group A: SCP — $19.0 \pm 1.6\%$, DCP — $10.7 \pm 1.3\%$; Group B: SCP — $11.7 \pm 0.8\%$, DCP — $4.8 \pm 0.8\%$; $p < 0.05$) and the choroid (Group A: choriocapillaris — $28.1 \pm 1.8\%$, choroid — $31.3 \pm 1.6\%$; Group B: choriocapillaris — $20.4 \pm 1.6\%$, choroid — $21.8 \pm 1.3\%$; $p < 0.05$), as well as significantly higher visual acuity (Group A: 0.7 ± 0.1 ; Group B: 0.5 ± 0.1 ; $p < 0.05$) and macular light threshold (Group A: $25.9 \pm 1.4 \text{ dB}$; Group B: $22.3 \pm 1.1 \text{ dB}$; $p < 0.05$) compared with the patients on PH. Thus, the normalization of carbohydrate metabolism and the mitigation of uremic syndrome in patients with T1DM and ESRF after SPK favorably affect the functional condition of the macular area, as indicated by the improvement in macular blood flow and visual functions.

Keywords: diabetes mellitus, diabetic retinopathy, diabetic nephropathy, simultaneous pancreas and kidney transplantation, optical coherence tomography angiography

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Compliance with ethical standards: the study was approved by Ethical Committee at the Russian Medical Academy of Continuous Professional Education (Protocol № 1 of January 18, 2021); the written informed consent for the study was provided by all participants.

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ГЕМОПЕРФУЗИЯ И ФУНКЦИОНАЛЬНОЕ СОСТОЯНИЕ МАКУЛЫ ПОСЛЕ СОЧЕТАННОЙ ТРАНСПЛАНТАЦИИ ПОЧКИ И ПОДЖЕЛУДОЧНОЙ ЖЕЛЕЗЫ

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Сочетанная трансплантация почки и поджелудочной железы (СТПиПЖ) — эффективный метод лечения больных с сахарным диабетом 1-го типа (СД1) и терминальной стадией хронической почечной недостаточности (ТХПН), который приводит к купированию гипергликемии и уремического синдрома. Целью работы было изучить морфофункциональное состояние и гемодинамику макулы у пациентов с СД1 после СТПиПЖ. В исследовании участвовали 45 пациентов, разделенных на три группы: в группу А вошли пациенты с СД1 после СТПиПЖ; в группу В — с СД1 и ТХПН, проходящие курсы программного гемодиализа (ПГД) и ожидающие СТПиПЖ; в группу С — лица, не имеющие глазных и системных патологий. Всем пациентам проводили традиционное офтальмологическое обследование, а также измерение центральной толщины сетчатки (ЦТС), среднего значения плотности перфузии в четырех сосудистых слоях: поверхностном (ПКСС) и глубоком (ГКСС) капиллярных сплетениях сетчатки, слое хориокапилляров (ХК) и хориоидеи. После СТПиПЖ, по сравнению с ПГД, выявлено уменьшение ЦТС (в группе А: $241 \pm 33 \text{ мкм}$; в группе В: $309 \pm 10 \text{ мкм}$; $p < 0,05$), увеличение среднего значения плотности перфузии сетчатки (в группе А: ПКСС — $19,0 \pm 1,6\%$, ГКСС — $10,7 \pm 1,3\%$; в группе В: ПКСС — $11,7 \pm 0,8\%$, ГКСС — $4,8 \pm 0,8\%$; $p < 0,05$) и хориоидеи (в группе А: ХК — $28,1 \pm 1,8\%$, хориоидея — $31,3 \pm 1,6\%$; в группе В: ХК — $20,4 \pm 1,6\%$, хориоидея — $21,8 \pm 1,3\%$; $p < 0,05$) в макулярной области, остроты зрения (в группе А: $0,7 \pm 0,1$; в группе В: $0,5 \pm 0,1$; $p < 0,05$) и порога светочувствительности макулы (в группе А: $25,9 \pm 1,4 \text{ дБ}$; в группе В: $22,3 \pm 1,1 \text{ дБ}$; $p < 0,05$). Нормализация углеводного обмена и купирование уремического синдрома у больных с СД1 и ТХПН после СТПиПЖ благоприятно влияют на состояние макулярной области в виде улучшения макулярного кровотока и зрительных функций.

Ключевые слова: сахарный диабет, диабетическая ретинопатия, диабетическая нефропатия, сочетанная трансплантация почки и поджелудочной железы, оптическая когерентная томография-ангиография

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About 10% of diabetes cases worldwide are classified as type 1 diabetes mellitus (T1DM). This most severe type of diabetes develops due to autoimmune damage to pancreatic β -cells. Up to 85% of T1DM cases are diagnosed in early adolescence. About 1,100,000 individuals aged under 20 currently live with T1DM, and the global prevalence continues to increase by about 132,600 new cases per annum [1]. In Russia, the prevalence of T1DM at the end of 2020 was 180.9 cases per 100,000 population [2].

Insulin therapy remains the main treatment for T1DM. The proper administration of insulin can mitigate the hyperglycemia and considerably prevent the onset and progression of diabetic complications [3]. However, according to the T1D Exchange registry, as little as 21% of patients with T1DM achieve the recommended levels of glycated hemoglobin (HbA1c) [4]. In this regard, complications of T1DM remain the leading causes of disability and death among the patients [5].

Diabetic nephropathy is the third leading cause of death, surpassed only by cardiovascular disorders and cancers. The patients with T1DM-associated nephropathy, which progresses to the end-stage renal failure (ESRF) over 15–20 years [6], become inevitably faced with the need for the kidney replacement therapy. The dialysis procedures are expensive and require specialized medical facilities, advanced equipment, and dedicated personnel training. Besides, these procedures are debilitating and entail side effects [7]. On the other hand, kidney transplants in T1DM have low efficacy due to the high risks of secondary nephropathy in posttransplantation period [8].

The simultaneous pancreas and kidney transplantation (SPK) is arguably the most advantageous treatment for the patients with T1DM-associated ESRF. The intervention normalizes carbohydrate metabolism and renal excretion, thereby liberating the patients from the constant glucose monitoring, insulin therapy, and debilitating hemodialysis courses [9].

This study aimed at the assessment of morphofunctional status of the macula and macular hemodynamics against the glycemia normalization and the mitigation of uremic syndrome in patients with T1DM after SPK.

METHODS

The study enrolled 45 participants (68 eyes). The inclusion criteria were T1DM-associated ESRF treated with either programmed hemodialysis (PH, group of comparison) or allogeneic pancreas-kidney transplants (main group), or the

absence of ophthalmic and systemic pathologies (control group). The non-inclusion criteria were type 2 diabetes and other systemic pathologies, ESRF of non-diabetic genesis, and the pancreas and/or kidney transplant rejection. Eyes with a history of retinal laser photocoagulation in the macular area, vitrectomy, cataract extraction, or panretinal laser photocoagulation performed less than 6 months before examination, as well as those with proliferative lesions of the macula, comorbid retinal pathologies, glaucoma, pronounced opacities of the optical media, or high-grade refractive errors were excluded from the study.

All patients were divided into three groups: Group A (main group) — patients with T1DM and functional pancreas-kidney transplants (15 individuals, 18 eyes) (Fig. 1); Group B (comparison group) — patients with severe decompensated T1DM and associated ESRF, on waiting list for SPK and currently on PH (15 individuals, 20 eyes); and Group C (control group) — individuals without ophthalmic or systemic pathologies (15 individuals, 30 eyes).

All patients were subject to the standard ophthalmological examination including the maximally corrected visual acuity (MCVA) and intraocular pressure tests, biomicroscopy of the anterior eye segment, indirect slit-lamp biomicroscopy with a 78-diopter aspheric lens, and photorecording funduscopy.

The measurements of central retinal thickness (CRT) and perfusion densities were carried out by optical coherence tomography (OCT) angiography in the RS-3000 Advance 2 system (NIDEK; Japan). The average perfusion density (PD) of the macular region (scan area 3.0–3.0 mm) was measured in four vascular layers: superficial and deep capillary plexuses of the retina (respectively, SCP and DCP), the capillary lamina of choroid (choriocapillaris), and choroid proper (Fig. 2) using AngioScan mode. The macular light threshold (MLT) was determined by Macular Integrity Assessment (MAIA) microperimetry (CenterVue S.p.A; Italy).

To assess the degree of T1DM compensation and renal functionality, all patients underwent blood tests for HbA1c, creatinine, and urea, providing the estimated glomerular filtration rate, eGFR.

The data were analyzed in StatTech v. 2.6.2 (StatTech; Russia). Quantitative indicators were assessed for compliance with the normal distribution using the Shapiro–Wilk and Kolmogorov–Smirnov criteria. Comparisons of quantitative indicators for three or more groups were carried out using one-way ANOVA and nonparametric Kruskal–Wallis test. Direction

Table. Comparative analysis of perfusion densities in four vascular layers of the macular region

Indicator	Group	M \pm SD	95% CI	n	p	
PD SCP (%)	A	19.0 \pm 1.6	17.0–21.0	18	Group A – Group B	<0.05*
	B	11.7 \pm 0.8	10.7–12.7	20	Group A – Group C	<0.05*
	C	34.3 \pm 1.0	33.6–35.4	30	Group B – Group C	<0.05*
PD DCP (%)	A	10.7 \pm 1.3	9.3–12.2	18	Group A – Group B	<0.05*
	B	4.8 \pm 0.8	3.8–5.8	20	Group A – Group C	<0.05*
	C	14.3 \pm 1.2	13.3–15.6	30	Group B – Group C	<0.05*
PD choriocapillaris (%)	A	28.1 \pm 1.8	25.7–30.5	18	Group A – Group B	<0.05*
	B	20.4 \pm 1.6	18.3–22.4	20	Group A – Group C	<0.05*
	C	45.7 \pm 0.8	45.0–46.4	30	Group B – Group C	<0.05*
PD choroid (%)	A	31.3 \pm 1.6	29.2–33.8	18	Group A – Group B	<0.05*
	B	21.8 \pm 1.3	20.2–23.4	20	Group A – Group C	<0.05*
	C	48.0 \pm 0.8	47.2–48.8	30	Group B – Group C	<0.05*

Note: PD SCP — perfusion density of the superficial capillary plexus of the retina; PD DCP — perfusion density of the deep capillary plexus of the retina; PD choriocapillaris — perfusion density of the choriocapillaris; PD choroid — perfusion density of the choroid; Group A — patients after the simultaneous pancreas and kidney transplantation (SPK); Group B — patients on PH/waiting list for the simultaneous pancreas and kidney transplantation (SPK); Group C — healthy individuals.

and strength of relationships between quantitative variables were described by Pearson's and Spearman's correlation coefficients.

RESULTS

A total of 24 women and 21 men aged 35 ± 7 years on average participated in the study. Groups A, B, and C were statistically similar with regard to gender ($p = 0.784$) and age ($p = 0.839$) of the participants. The average length of time since the diagnosis of T1DM in Groups A and B was 27 ± 8 years, similar between the groups ($p = 0.475$). Patients with pre-proliferative (PPDR) and proliferative (PDR) stages of diabetic retinopathy were encountered in both groups, all of them previously treated with panretinal laser photocoagulation. The incidence of PPDR and PDR between the groups was similar ($p = 0.756$). The average time since transplantation in Group A was 21 ± 11 months. The average time on PH in Group B was 24 ± 8 months.

Comparison of CRT measurements for the three groups revealed statistically significant differences ($p < 0.05$). In patients with decompensated T1DM on PH, the central portion of the retina was thicker (Group B, $309 \pm 10 \mu\text{m}$) than in patients after SPK (Group A, $241 \pm 33 \mu\text{m}$) or healthy individuals (Group C, $260 \pm 6 \mu\text{m}$).

The highest average perfusion density of the retina and choroid was observed in the control group (Group C). The patients with transplants (Group A) had higher perfusion rates of the retina and choroid than the patients on PH/waiting list for SPK (Group B) (Table).

Both MCVA and MLT were significantly higher in the patients with pancreas-kidney transplants (Group A: MCVA — 0.7 ± 0.1 , MLT — 25.9 ± 1.4 dB) than in the patients with decompensated T1DM on PH (Group B: MCVA — 0.5 ± 0.1 , MLT — 22.3 ± 1.1 dB; $p < 0.05$) (Fig. 3).

All three groups revealed pronounced correlations between indicators of the functional state of the macula and perfusion density of the retina and choroid. MCVA positively correlated with the choriocapillaris perfusion density ($p = 0.886$; $p < 0.05$), whereas MLT positively correlated with PD SCP ($p = 0.772$; $p < 0.05$).

HbA1c levels in the patients with transplants were significantly reduced compared with the patients on PH (Group A — $4.8 \pm 0.4\%$; Group B — $7.1 \pm 0.8\%$; $p < 0.05$). Both CRT and PD SCP correlated with the hemoglobin glycation levels: higher levels of HbA1c were accompanied by increased CRT ($p = 0.848$; $p < 0.05$) and decreased SCP perfusion density ($r = -0.723$; $p < 0.05$).

Low perfusion densities for both DCP and choriocapillaris in Group B significantly correlated with the renal functionality indicators (Fig. 4). In particular, creatinine levels negatively correlated with DCP perfusion density ($p = -0.758$; $p < 0.05$), whereas eGFR positively correlated with the choriocapillaris perfusion density ($p = 0.867$; $p < 0.05$).

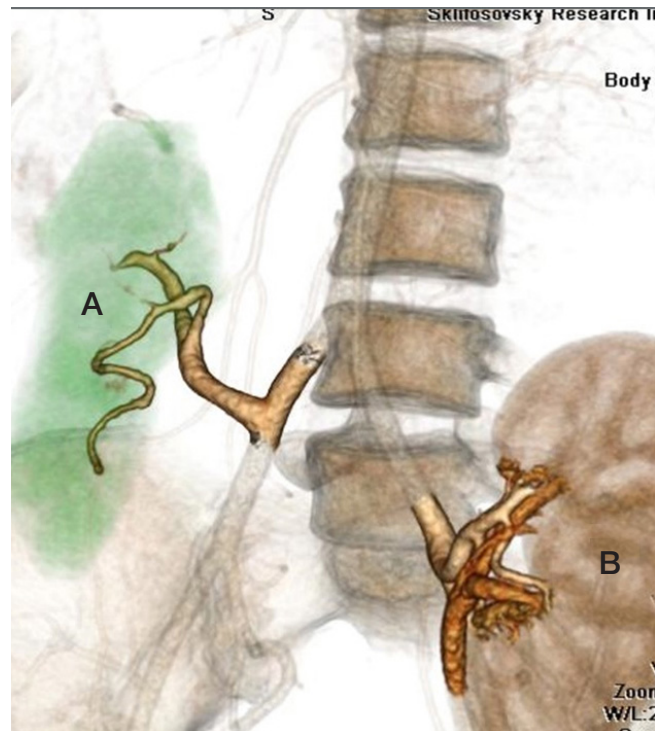


Fig. 1. Computed tomography image with intravenous contrast, 3D reconstruction, showing typical positions of the pancreatic (A) and kidney (B) transplants in the recipient

DISCUSSION

The majority of studies on the condition of the retina after SPK, published in recent decades, assessed the clinical manifestations of diabetic retinopathy (DR) using ophthalmoscopy and fluorescent angiography. These studies demonstrated stabilization and improvement in the condition, manifesting as a reduced need for laser photocoagulation of the retina and vitrectomy in more than 60% of the cases [10–13]. The improvement in the ophthalmoscopic picture, noted in 21.3–41.7% of the patients, was accompanied by a decrease in the grade of hard and soft exudates and intraretinal microvascular abnormalities [14, 15]. An improvement in visual acuity in patients with proliferative DR after SPK was also reported [16].

The advent of modern ophthalmological diagnostic equipment (OCT angiography and microperimetry) enabled detailed investigation of hemodynamics and morphofunctional state of the retina in patients with DR after various treatments [17–21]; however, we failed to find any published evidence on the dynamics of retinal hemoperfusion and light sensitivity in DR after SPK.

Our patients on waiting list for SPK had significantly higher CRT ($309 \pm 10 \mu\text{m}$) and significantly lower average perfusion

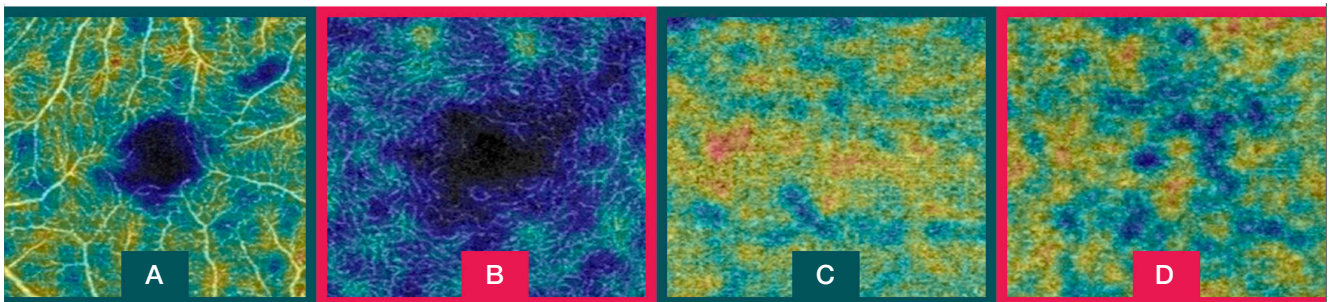


Fig. 2. Perfusion density measured in four vascular layers of the macular region (color-coded OCT angiography, RS-3000 Advance 2 system, NIDEK, Japan). (A) Superficial capillary plexus of the retina. (B) Deep capillary plexus of the retina. (C) Choriocapillaries. (D) Choroid

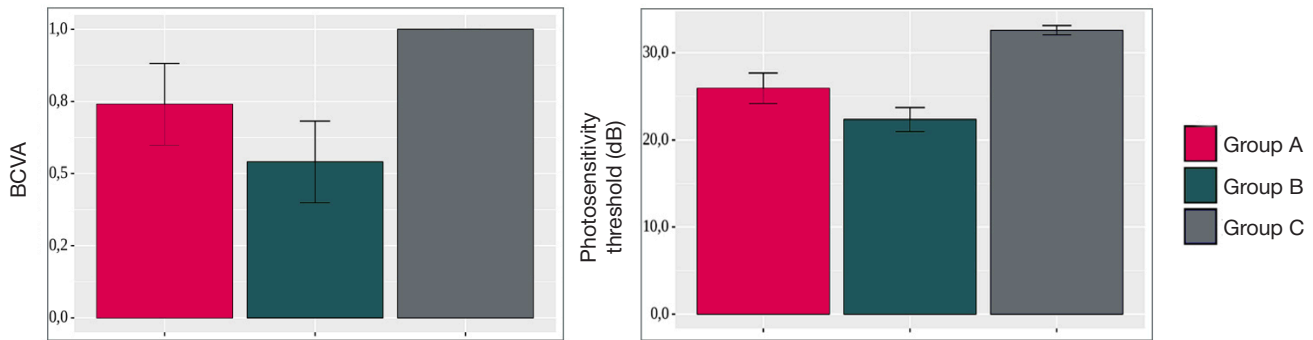


Fig. 3. Analysis of functional indicators for the macular region. BCVA — best corrected visual acuity. Group A — patients after simultaneous kidney and pancreas transplantation. Group B — patients awaiting simultaneous kidney and pancreas transplantation. Group C — healthy patients

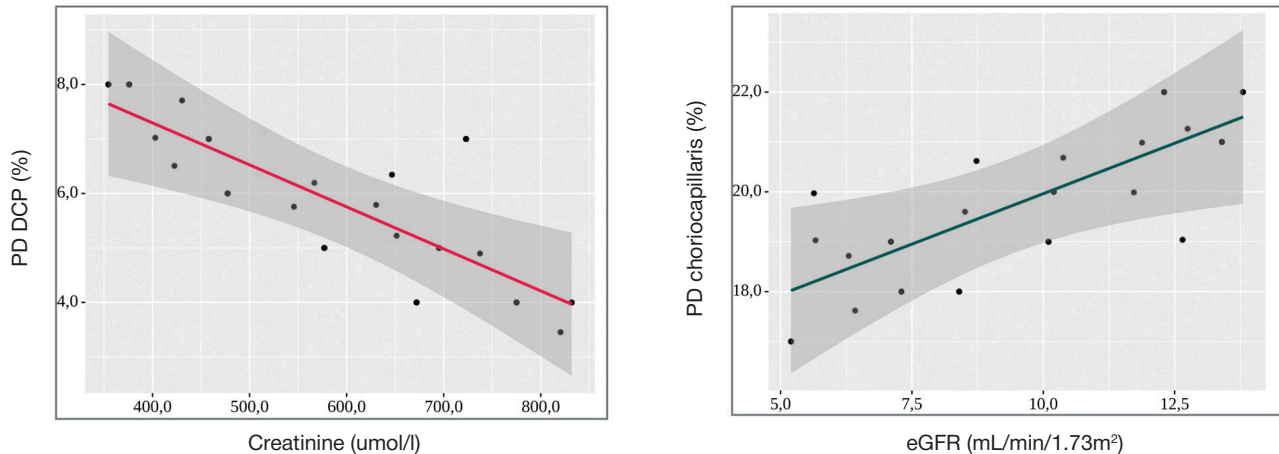


Fig. 4. Regression plots showing correlations of DCP and choriocapillaris perfusion densities with creatinine levels and eGFR, respectively. PD DCP — perfusion density of the deep capillary pexus. PD — perfusion density. EGFR — estimated glomerular filtration rate

density in four macular layers (PD SCP — $11.7 \pm 0.8\%$; PD DCP — $4.8 \pm 0.8\%$; PD choriocapillaris — $20.4 \pm 1.6\%$; PD choroid — $21.8 \pm 1.3\%$) than patients after SPK (Group A: CRT — $241 \pm 33 \mu\text{m}$; PD SCP — $19.0 \pm 1.6\%$; PD DCP — $10.7 \pm 1.3\%$; PD choriocapillaris — $28.1 \pm 1.8\%$; PD choroid — $31.3 \pm 1.6\%$; $p < 0.05$). CRT, macular perfusion density, as well as the laboratory blood test indicators of T1DM decompensation and renal functionality (HbA1c, creatinine, eGFR), revealed significant correlations. Normalization of glucose levels and mitigation of uremia in the aftermath of SPK are beneficial for the peripheral microcirculation. In particular, it results in stronger vascular walls and decreased extravasation of blood plasma and formed elements to the intervascular spaces of ocular tissues, with the resulting reduction in retinal thickness and enhanced hemoperfusion in retina and choroid of the eye. The improved morphometric parameters (reduced CRT)

and macula hemoperfusion indicators (increased perfusion density in four vascular layers) are directly related to the improvement in visual functions (as assessed through MCVA and retinal light sensitivity measurements) in the post-transplantation period.

CONCLUSIONS

The advanced diagnostics involving the non-invasive OCT angiography and fundus-microperimetry enables the accurate functional assessment of the macular region in patients with T1DM before and after SPK. The study demonstrates significant improvement in macular hemoperfusion and morphofunctional status of the macula, as well as improved visual acuity in the post-transplantation period, compared with the patients on waiting list for a similar transplantation.

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