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The results of kidney transplantation in elderly recipients with diabetes mellitus

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Introduction. *Currently, the type 2 diabetes mellitus is in the nature of an epidemic of non-infectious etiology. In this regard, the incidence of diabetes mellitus complications, including diabetic nephropathy, which lead to end-stage chronic renal disease, is also increasing. The treatment of type 2 diabetic patients with end-stage chronic renal disease presents significant difficulties, which is associated with an additional risk of*

developing infectious complications and, as a rule, the presence of concomitant pathology of the cardiovascular system.

Objective: *to analyze the results of kidney transplantation in elderly patients with diabetes mellitus in the early postoperative period.*

Material and methods. *The study is based on a retrospective analysis of the results of 77 kidney transplantations performed to elderly recipients at N.V. Sklifosovsky Research Institute for Emergency Medicine in the period from 2015 to 2019. The study group included 22 recipients over 60 years old with type 2 diabetes mellitus, as main or concomitant disease. The comparison group consisted of 55 recipients over 60 years without diabetes.*

Results. *Survival of recipients with type 2 diabetes mellitus was significantly lower (p = 0.026). So, there were 20 surviving recipients (90.9%) in the group of patients with type 2 diabetes mellitus, and 55 (100%) surviving recipients in the group without diabetes. When comparing the kidney graft survival rates in the recipients between the two groups, no statistically significant difference (p = 0.29) was found. The overall graft survival was 77.3% (n = 17) in the group of recipients with type 2 diabetes mellitus, and 89.1% (n = 49) in the comparison group.*

Conclusions. *It has been proven that kidney transplant recipients with type 2 diabetes mellitus have a significantly lower survival rate after transplantation than recipients without diabetes; and the kidney graft survivals were not significantly different early after transplantation. The recipients did not show differences in the recovery of the transplanted kidney function depending on the presence of type 2 diabetes mellitus.*

Keywords: type 2 diabetes mellitus, kidney transplantation, recipients over 60 years old

DM, Diabetes mellitus

ESRD, end-stage chronic renal disease

HLA, major histocompatibility complex

RAG, renal allograft

T2DM, type 2 diabetes mellitus

Introduction

Diabetes mellitus (DM) and chronic renal disease are two global medical problems today [1]. The constant increase in the incidence and progression of complications of type 2 diabetes (T2DM) is regarded by experts of the World Health Organization as an epidemic of non-infectious etiology predisposed by social and economic processes and changes in a human lifestyle (decreased physical activity), improper (excessive) nutrition [2]. There are more than 450 million patients suffering DM in the world, and T2DM makes up 90% of the total number of cases [3]. At the same time, experts suggest that the data of official statistics on diabetes is 2-3 times lower than the actual prevalence of the disease, due to the fact that the request for medical care occurs much later than the onset of the disease [2, 4]. As a result, from one third to half of the T2DM cases remain undiagnosed, since they have not clinically manifested themselves for several years [3]. The incidence of diabetic nephropathy development directly depends on the disease duration: for example, it makes 7–10% with the T2DM duration not exceeding 5 years, and 50–57% in T2DM persisting over 25 years [5, 6]. There is a widespread prevalence of T2DM among people over 65 years of age. According to 2017 data, the number of people with T2DM aged 65–99 years is 122.8 million, which corresponds to 18.8% [3].

Renal pathology in glomerulonephritis, in drug nephropathy, urinary tract infections, hypertensive nephrosclerosis, etc., unlike diabetic

nephropathy, has a different pathogenesis and course of the disease, which is a serious problem for patients with T2DM, since it is aggravated. The treatment of type 2 diabetes patients with end-stage chronic renal disease (ESRD) presents significant difficulties, being associated with an additional risk of developing infectious complications and, as a rule, the presence of concomitant cardiovascular system pathology. Mortality in this patient population is significantly higher than in patients without diabetes [7, 8]. Therefore, a few years ago, diabetic nephropathy was considered as a relative or absolute contraindication to kidney transplantation. However, the mortality rate in the patients with DM receiving a hemodialysis replacement therapy has been significantly higher compared with the results in patients without diabetes and after kidney transplantation. Patients with DM are at a higher risk of death from cardiovascular disease than patients without diabetes, especially under the age of 50 years old. Currently, about 40% of recipients awaiting transplantation on the waiting list are the DM patients [9, 10]. F.G.Cosio et al. compared the risk of cardiovascular complications in kidney transplant recipients with DM and without it and showed that the DM patients had a lower 5-year survival rate of 70 versus 93% ($p < 0.001$, statistically significant in both groups) and a higher rate of cardiovascular complications (37% versus 9%) ($p < 0.001$, statistically significant in both groups) [1]. In a similar study, P.Boucek described that the 1-year and 5-year recipient survivals made 85 and 74% versus 84 and 69% ($p = 0.43$), while the graft survival censored for patient death was 84 and 77% versus 82 and 77% for patients with diabetes and without it, respectively ($p = 0.52$). Thus, there were no differences in a 1-year recipient survival, as none in the graft survival [11]. No differences were later confirmed in the recipient and graft survivals during the first year and 5 years in kidney recipients with diabetes and without it in C.H.Baek studies. In addition,

the latter indicates no differences in the course of the early postoperative period [12]. In a large study (of over 10,000 recipients after kidney transplantation, of whom the DM patients accounted for 9%), W.H.Lim et al. indicated that mortality rates in the first 10 years after transplantation were higher in DM recipients (25.3%) compared to the data for similar end-points in recipients without diabetes (11.5%). Renal transplant recipients with T2DM had significantly lower survival, with a 5-year mortality rate being 2 times higher compared to patients without diabetes [13]. Given the published data, conducting one's own original study seems relevant.

The study objective was to analyze the results of kidney transplantation in elderly patients with diabetes mellitus in the early postoperative period.

Material and methods

The study was based on a retrospective analysis of the results of 77 kidney transplants performed in elderly recipients at N.V. Sklifosovsky Research Institute for Emergency Medicine from 2015 to 2019. The inclusion criterion was the patient's age of 60 years and older at the time of surgery. The exclusion criterion was the repeated nature of transplantation. The criterion for the patient allocation in groups was the presence/absence of diabetes mellitus. The study group (I) included 22 recipients over 60 years old with an underlying or concomitant disease of T2DM, and the comparison group (II) consisted of 55 recipients older than 60 years without diabetes mellitus.

The recipients of both groups did not significantly differ by sex, age, body mass index, sensitization to antigens of the major

histocompatibility complex (HLA), and the replacement therapy duration (Table. 1).

Table 1. Key characteristics of kidney recipients

Parameters	Number of recipients, n			p
	All the subjects studied 77	Group I (Study group) 22	Group II (Comparison group) 55	
Male, % (n) Female, % (n)	48.1 (37) 51.9 (40)	63.6 (14) 36.4 (8)	41.8 (23) 58.2 (32)	0.13
Age, years m (25; 75%) (min – max)	63 (61; 66) 60–77	63 (61; 66) 60–69	63 (61; 66) 60–77	0.87
Body mass index m (25; 75%)	27.1 (24.2; 31.4)	29.2 (24.2; 33.2)	32.4 (23.7; 31.2)	0.21
Pre-dialysis transplantation, % (n)	14.3 (11)	27.3 (6)	9.1 (5)	0.07
Duration on dialysis, days* m (25; 75%)*	972 (706; 1491)	1425 (794; 1945)	958 (673; 1206)	0.07
The presence of anti-HLA antibodies,% (n):	7.8 (6)	0	10.9 (6)	0.17

* calculation for recipients who received dialysis before transplantation, 16 people in Group I, 50 people in Group II

There were differences between the groups with regard to the nature of the underlying disease that caused the ESRD development (Fig. 1).

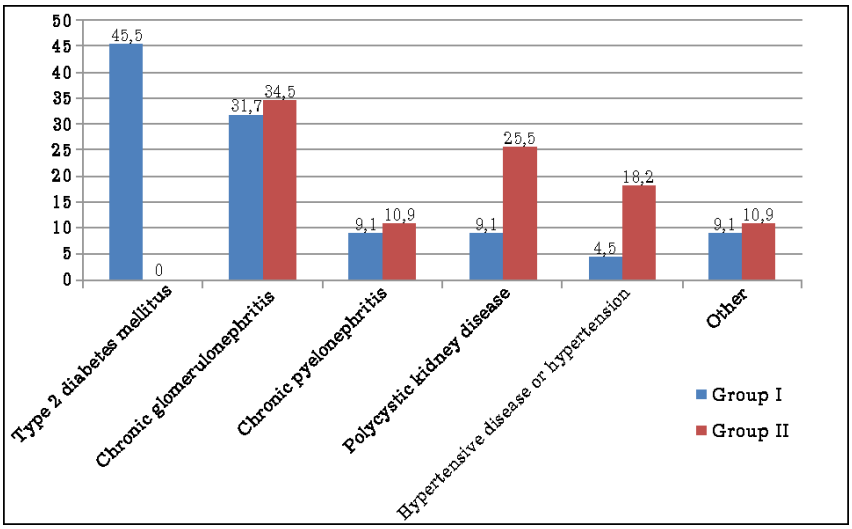

Fig. 1. Characterization of recipient groups by the underlying disease

Significant differences when comparing donor and operative factors between the recipients of the studied groups were seen only in the number of incompatible HLA-system antigens (Table. 2). So, there were fewer mismatches in the group of renal allograft (RAG) recipients with T2DM, than in that of the recipients without DM. When assessing the gender, age, cause of donor death, and the cold ischemia time for the graft, no differences between the groups were noted.

Table 2. Characterization of the groups by donor and operational factors

Parameters	Number of transplantations			p
	All 77	Group I 22	Group II 55	
Donor's gender: Male, % (n) Female, % (n)	 66.2 (51) 33.8 (26)	 72.7 (16) 27.3 (6)	 63.6 (35) 36.4 (20)	 0.59
Donor age, years, m (25; 75%) (min – max)	21–69 57 (51; 60)	21–69 54 (50; 59)	39–69 57 (52; 61)	0.10
Cause of donor's death:				

ACVA,% (n) TBI, % (n)	88.3 (68) 11.7 (9)	77.3 (17) 22.7 (5)	92.7 (51) 7.3 (4)	0.11
Cold ischemia time, hours, m (25; 75%) (min – max)	 8–26 13.5 (11; 15)	 10-26 12 (11; 15)	 8–19.5 13.5 (11; 15)	0.66
The number of HLA mismatches, m (25; 75%)	4 (3; 4)	3 (3; 4)	4 (3; 5)	0.018

Notes: ACVA: acute cerebrovascular accident; TBI: traumatic brain injury

Immunosuppressive therapy: in patients of both groups, calcineurin inhibitors (cyclosporin, tacrolimus), antiproliferative agents (mycophenolate mofetil or everolimus), and corticosteroids were used as baseline immunosuppression (Table 3). Chimeric monoclonal anti-CD25 antibodies (basiliximab) and polyclonal antibodies - antithymocytic immunoglobulin (ATGAM, thymoglobulin) were used in most recipients for the prevention of acute rejection. In case of acute rejection, the treatment was started with pulse therapy with methylprednisolone; if there was no effect, polyclonal antibodies and/or plasmapheresis procedures were prescribed. There were no differences in immunosuppression therapy between the recipients of two groups.

Table 3. Characterization of the groups by the immunosuppressive therapy used

Parameters		Number of transplantations			p
		All 77	Group I 22	Group II 55	
Baseline immunosuppression					
Calcineurin inhibitors	Cyclosporin A, % (n)	75.3 (58)	86.4 (19)	70.9 (39)	0.24
	Tacrolimus, % (n)	24.7 (19)	13.6 (3)	29.1 (16)	0.24
Antiproliferative	Mycophenolate mofetil, % (n)	89.6 (69)	90.9 (20)	89.1 (49)	1.00

agents	Everolimus, % (n)	10.4 (8)	9.1 (2)	10.9 (6)	1.00
Corticosteroids	Methylprednisolone, % (n)	100 (77)	100 (22)	100 (55)	> 0.05
Induction immunosuppression					
Monoclonal antibodies	Anti-CD25 (basiliximab), % (n)	50.6 (39)	54.5 (12)	49.1 (27)	0.80
Polyclonal antibodies	Antithymocytic globulin, % (n)	22.1 (17)	18.2 (4)	23.6 (13)	0.76
Without induction, % (n)		27.3 (21)	27.3 (6)	27.3 (15)	1.00

Monitoring period: the length of hospital stay from the moment of surgery to discharge. The results were considered positive when the recipient was discharged having a functioning RAG, and negative if the patient had to be returned to dialysis (transplantectomy or no prospects for graft function recovery as assessed by histological findings) or died.

Tests. The following instrumental diagnostic techniques were used to assess renal graft function: RAG ultrasonography and Doppler studies, dynamic angionephroscintigraphy. Biochemical parameters of blood and urine were assessed. To verify the cause of transplant dysfunction, a RAG biopsy was performed followed by a light microscopy and immunohistochemical examination. Computed tomography with intravenous contrast enhancement was performed if the development of vascular complications was suspected.

Statistical analysis of the obtained data was carried out using the Statistica for Windows v.10.0, Stat Soft Inc. software package (USA). The normality of the distribution was assessed by the Shapiro–Wilk test. The groups were compared using the Mann-Whitney test, Fisher's exact (two-sided) test, χ^2 test for arbitrary tables. Kaplan–Meier estimator method and log-rank test were used to assess survival. The differences were considered statistically significant at $p < 0.05$.

Results and discussion

When assessing the results of kidney transplantation using the $\chi 2$ test for arbitrary tables, we did not reveal any statistically significant differences between the recipients of two groups, however, an obvious relationship was found between the DM factor and the obtained results (Table 4).

Table 4. The final results

Parameters	Number of recipients, n			p
	All 77	Group I 22	Group II 55	
Discharged with a functioning RAG, % (n)	84.4 (65)	77.3 (17)	87.3 (48)	0.075
Discharged to dialysis, % (n)	13.0 (10)	13.6 (3)	12.7 (7)	
Died, % (n)	2.6 (2)	9.1 (2)	0	

Negative results were noted in 12 (15.6%) of all the studied kidney recipients. In half (50%) of cases, negative results were associated with a primary graft non-function due to kidney transplantation from an expanded criteria donor with severe nephrosclerosis that was morphologically confirmed subsequently. Vascular thrombosis developed in 2 cases (16.6%): that of the renal vein in one case, and artery thrombosis in the other, against the background of atherosclerotic altered renal arteries of the graft; a primary infected graft development and urinary infection with ureterocystoanastomosis incompetence were noted in 1 case each (8.3%), which led to the need for transplantectomy. In 2 cases (16.6%), the graft loss occurred due to recipient's death from cardiovascular complications in the presence of diabetes mellitus.

The cumulative proportion of kidney recipient survivors in both groups on day 18 was 0.97. When comparing the recipient survivals between the groups in the early postoperative period, using a log-rank test, we found that the T2DM recipient survival was statistically significantly lower (p = 0.026). So, there were 20 surviving recipients (90.9%) in the T2DM patient group, and 55 (100%) in the group without diabetes. Figure 2 shows the cumulative proportion of surviving recipients in the early postoperative period by groups.

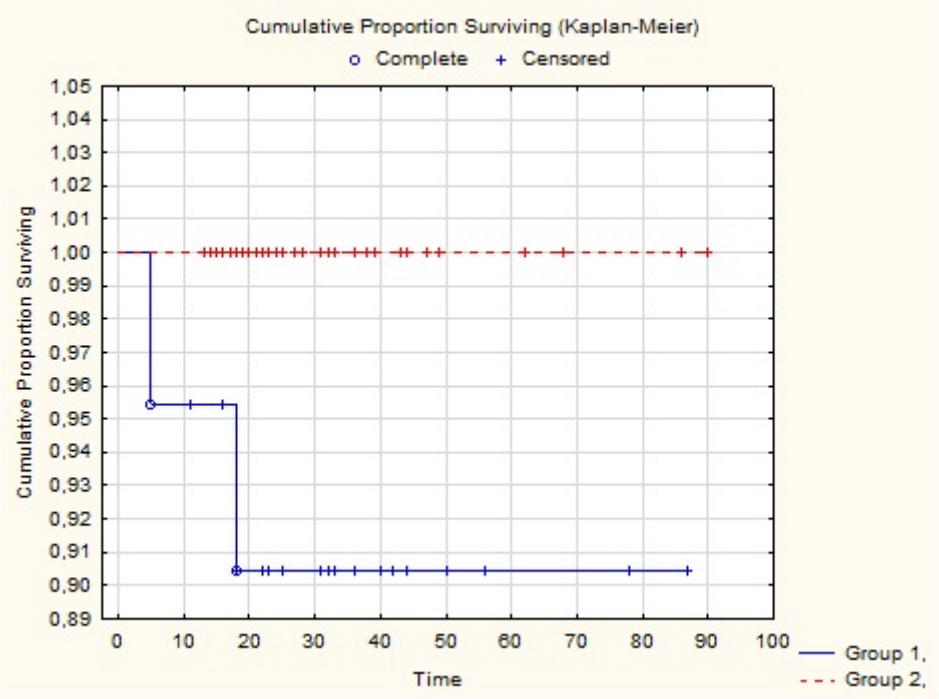

Fig. 2. Cumulative proportion of surviving kidney recipients in the studied groups

The total cumulative proportion of kidney graft survivals in recipients of both groups on day 25 after surgery was 0.87. When comparing the kidney graft survivals in the recipients between the two groups, no statistically significant difference (p = 0.29) was found. The graft survival was 77.3% (n = 17) in the T2DM recipient group, and 89.1% (n = 49) in the group without diabetes. Figure 3 shows the

proportion of surviving kidney grafts in elderly recipients by groups in the early postoperative period.

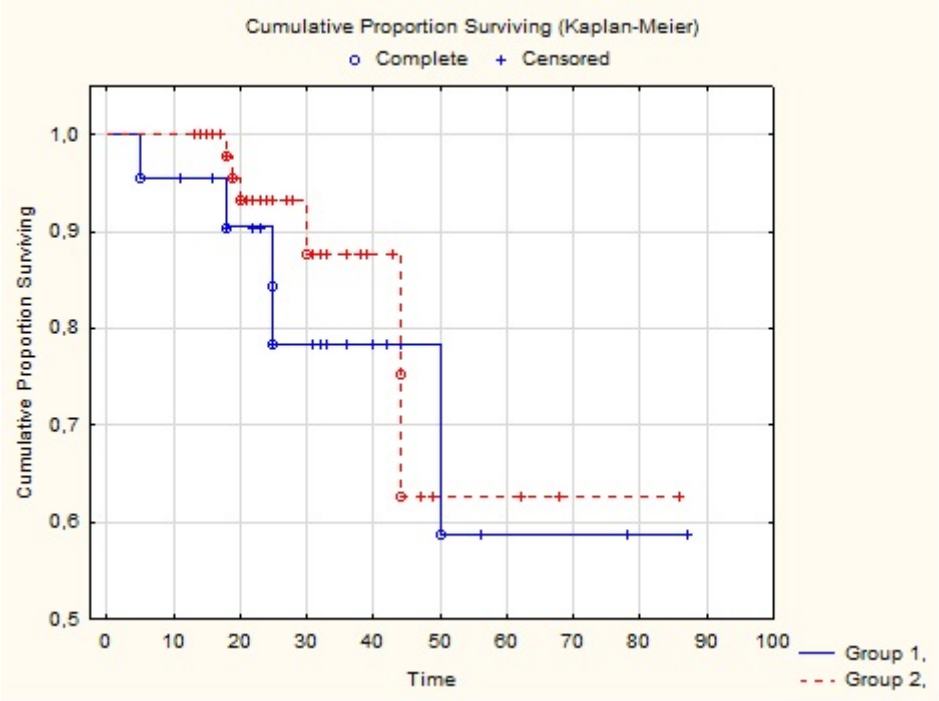

Fig. 3. Cumulative proportion of surviving kidney grafts in the recipients of the studied groups

The hospital length of stay averaged 32 days (23; 43) in recipient group I, and 22 days (19; 36) in group II, p = 0.14.

The immediate primary renal graft function was observed in half of the recipients in both groups (Fig. 4).

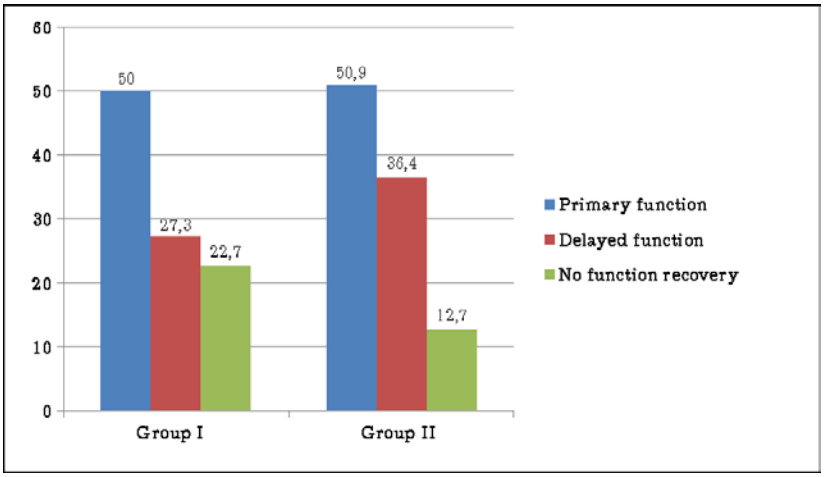

Fig. 4. Primary renal graft function in the studied groups

There were no statistically significant differences between the groups in the incidence of the delayed RAG function and no RAG function recovery (p = 0.5).

No statistically significant differences were found between the groups when assessing the final renal graft function in patients.

Table 5. The final renal allograft function in the recipients of both groups at discharge

Parameters	Number of recipients*, n			p
	All 65	Group I 17	Group II 48	
Blood creatinine, mcmol/L, m (25; 75%) min-max	71–408 152 (121; 226)	81–288 160 (121; 226)	71–408 150 (122; 199)	0.79
Blood urea, mmol/L, m (25; 75%) (min – max)	4.8–46 11.5 (8.7; 17)	4.8-23 12 (8.7; 19)	4.8–46 11.1 (8.8; 16)	0.81
Glomerular filtration rate, ml/min, m (25; 75%) (min – max)	9-85 38 (29; 46)	14–85 36 (29; 52)	9-78 38 (28; 44.5)	0.93

* Patients with graft non-function and the dead are excluded

Kidney transplantation for patients with type 2 diabetes mellitus is now becoming more widely used. This is due to the expansion of the criteria both for donors and recipients. In 2015–2018, in the N.V. Sklifosovsky Research Institute for Emergency Medicine, 28.6% of all kidney recipients over 60 years old had type 2 diabetes mellitus as the underlying or concomitant disease, which indicates a high incidence of this disease among elderly patients. The reduced survival of kidney transplant T2DM recipients in the early postoperative period has been associated with the development of cardiovascular system complications and is comparable with the results published by foreign colleagues. The lower graft survival rates in the recipients of both groups compared to world data were due to kidney transplant with donor pathology in 50% of cases, which prompts the need for a more thorough assessment of donor organs using preliminary kidney biopsy in all expanded criteria donors.

Conclusions

1. The recipient survival in kidney transplant recipients with type 2 diabetes mellitus in the early post-transplant period is significantly lower than in kidney transplant recipients without diabetes.

2. The kidney graft survival in the early post-transplant period between elderly recipients with type 2 diabetes mellitus and without it does not differ significantly.

3. No statistically significant differences were seen in the transplanted kidney function recovery between the recipients older 60 years with type 2 diabetes and without it.

4. No statistically significant differences in the in-hospital treatment duration, glomerular filtration rate, creatinine and urea levels were noted between the elderly kidney recipients with type 2 diabetes and without it.

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