There are no relevant conflicts of interest to disclose.

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Diabetic Kidney Transplant Recipients: Impaired Infection Control and Alloreactivity

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INTRODUCTION

Overall, studies that use the current criteria for diagnosis of new onset diabetes after transplantation suggest that approximately one-third of nondiabetic kidney transplant recipients develop persistently impaired glucose metabolism by six months posttransplantation. The prevalence of NODAT at one year following transplantation appears to be approximately 10% depending on the immunosuppressive agents used. Many of the same risk factors that predispose nontransplant patients to diabetes mellitus have been identified as risk factors for its development after transplantation. Such common risk factors include age, obesity, ethnicity, family history, or the presence of HCV. In addition, some risk factors are unique to the transplant population. These include specific agents used for immunosuppression, HLA mismatches, donor sex, and the type of the underlying renal disease as polycystic kidney disease. Firstly, the presence of pre-existing diabetes or NODAT has been associated with an increased risk for infection and sepsis. Secondly, pre-existing diabetes and NODAT have been suggested to decrease long-term allograft survival. Thirdly, pre-existing diabetes and NODAT have been associated with increased mortality rates.

PATIENTS AND METHODS

We performed an analysis of 775 kidney transplant recipients (KTRs). 80 KTRs (10.3%) were diagnosed with NODAT. NODAT has been diagnosed by random and fasting plasma glucose measurements. 114 KTRs (14.7%) were diagnosed with pre-existing diabetes among which 34 patients were under oral hypoglycemic drugs and 80 patients under insulin treatment. For comparison an age-, gender-, and maintenance immunosuppression-matched control group of 208 KTRs was used. Samples were collected before transplantation and at +1, +2, and +3 months posttransplantation. Lymphocyte subpopulations were measured by flow cytometry. CMV-specific and alloreactive T-cells were measured using an interferon-γ Elispot assay.

	NODAT (n=80)	pre-existing diabetes (n=114)	non-diabetes (matched) (n=208)	*P value*
Age, years [median (range)]	57 (18-76)	60 (18-76)	58 (18-77)	*0.685*
Male sex, n (%)	55 (69)	81 (71)	149 (71)	*0.891*
BMI >30, n (%)	15 (19)	36 (32)	15 (7)	*<0.001**
Time on dialysis, months [median (range)]	63 (0-142)	47 (0-194)	52 (0-139)	*0.148*
CMV viremia, n (%)	36 (45)	40 (35)	65 (31)	*0.091*
BK viremia, n (%)	8 (10)	10 (10)	17 (8)	*0.887*
EBV viremia, n (%)	7 (9)	12 (11)	18 (9)	*0.848*
Septic complications, n (%) Severe sepsis/septic shock	16 (20) 4 (5)	19 (17) 8 (7)	13 (6) 5 (2)	*0.001**
Infection as cause of death, n (%)	6 (8)	11 (10)	4 (2)	*0.007**
Delayed Graft Function, n (%)	22 (28)	47 (41)	48 (23)	*0.002**
Tacrolimus/MMF/steroid, n (%)	67 (84)	85 (75)	164 (79)	*0.306*
IL-2 receptor antagonist, n (%)	69 (86)	103 (90)	183 (88)	*0.647*
Acute rejection, n (%) Borderline/IA/IB IIA/IIB/III	32 (40) 25 (31) 7 (9)	29 (26) 21 (18) 8 (7)	54 (26) 39 (19) 15 (7)	*0.048**
Donor age, years [median (range)]	57 (17-85)	56 (21-82)	55 (11-84)	*0.782*

RESULTS

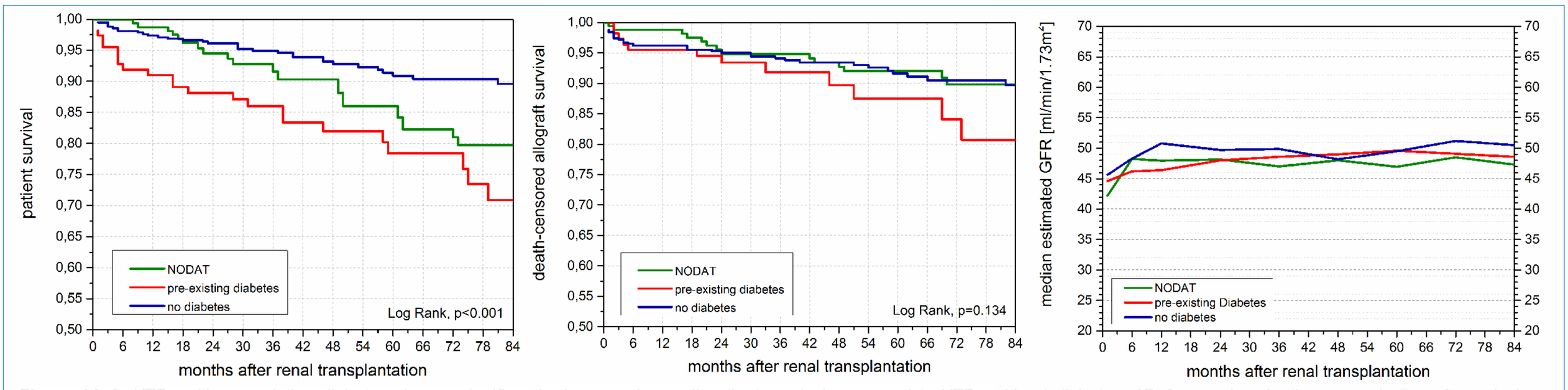
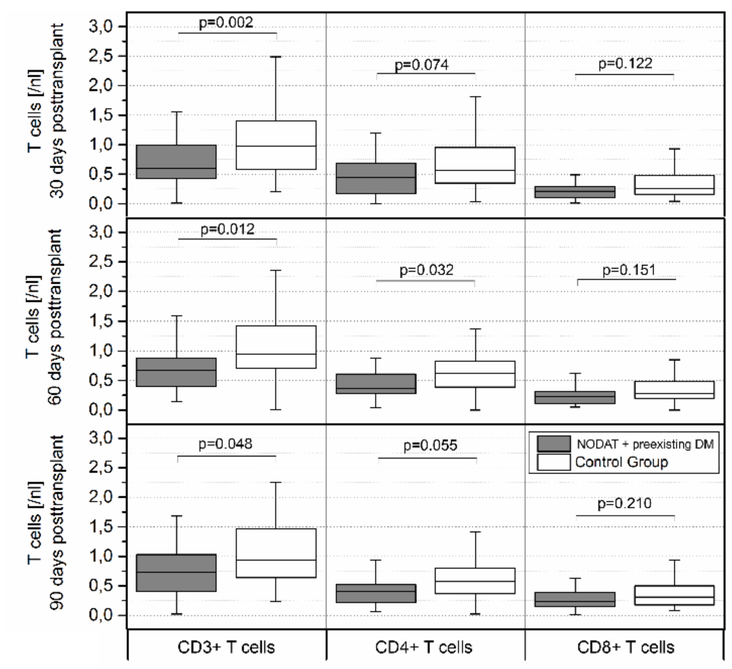
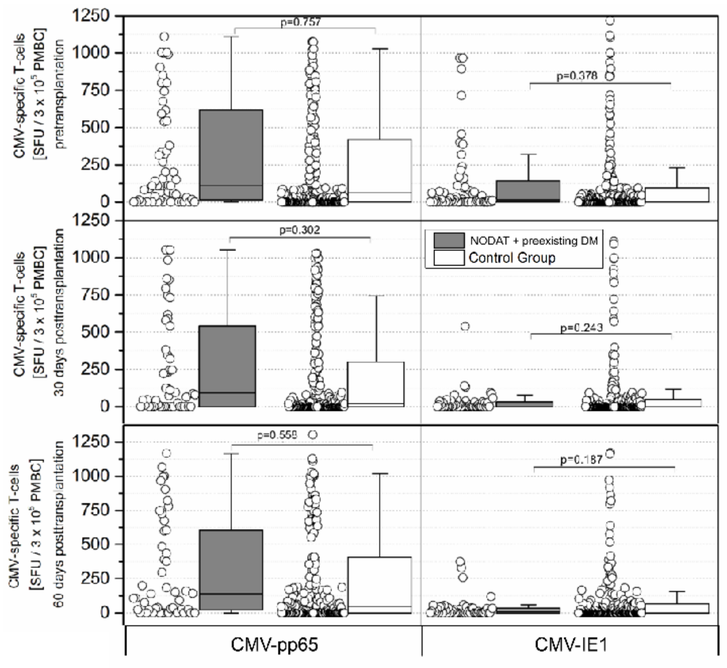


Figure 1A-C. KTRs with pre-existing diabetes show a significantly decreased overall patient survival compared to KTRs without diabetes. **1B** Concerning death-censored allograft survival, no statistical significant differences were observed between KTRs with pre-existing diabetes, NODAT, and KTRs without any diabetes. **1C** Concerning estimated GFR, no statistical significant differences were observed between KTRs with pre-existing diabetes, NODAT, and KTRs without any diabetes.





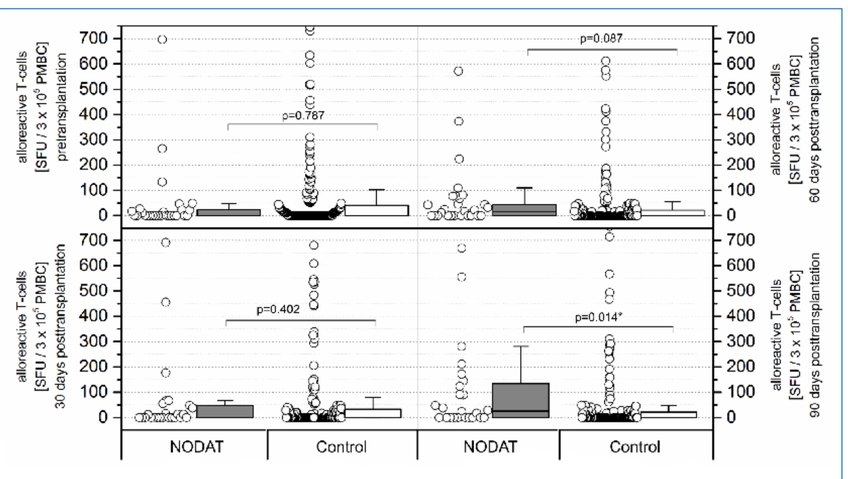


Figure 2A-C. 2A Total CD3+ and CD4+ T-cell counts were significantly lower in KTRs with pre-existing diabetes and NODAT ($p<0.05$). **2B** No differences were observed for CMV-specific T-cells ($p>0.05$). **2C** KTRs developing NODAT showed an increase in alloreactive T-cells compared to KTRs without diabetes ($p<0.05$).

CONCLUSIONS

1. **KTRs with pre-existing diabetes and NODAT show a significantly increased risk for the development of severe infection and sepsis compared to the control group.** Here our data show, that hyperglycemia might alter overall immunity. CD3 and CD4 lymphopenia may contribute to the increased risk of severe infection and sepsis.
2. **KTRs with pre-existing diabetes and NODAT show a significantly increased risk of infection-related mortality compared to the control group.** Here our data show, that hyperglycemia might alter overall immunity. CD3 and CD4 lymphopenia may contribute to the increased risk of infection-related mortality in kidney transplant recipients.
3. **KTRs with pre-existing diabetes and NODAT show no differences for virus-specific immunity compared to the control group.** Here our data show no differences for CMV-specific cellular immunity directed to CMV-pp65 and CMV-IE1.
4. **KTRs developing NODAT show significantly higher rates of acute cellular rejections.** This may be attributed to the increased frequencies of alloreactive T-cells in the early posttransplant period. Therefore maintaining adequate immunosuppression to prevent acute cellular rejection is of major importance in kidney transplant recipients developing NODAT. In our experience, efforts to decrease diabetogenic immunosuppressive therapy in order to prevent NODAT should not be undertaken even at the expense of the development of NODAT.

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