There are no relevant conflicts of interest to disclose.

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# Adverse Outcomes in Obese Kidney Transplant Recipients Are Limited to Those with Diabetes Mellitus

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## INTRODUCTION

The importance of obesity and morbid obesity has increased as a cause of morbidity and mortality worldwide over the last decades. In this context a high body mass index (BMI) has been associated with multiple comorbid conditions as hypertension, coronary artery disease and in particular diabetes, that further increase the risk of cardiovascular disease and cardiovascular mortality. Previous studies suggest no relation between obesity and negative outcomes after kidney transplantation, but suggest similar patient and only slightly inferior allograft survival compared to kidney transplant recipients (KTRs) with normal BMI. Much more previous studies suggest, that obese KTRs benefit from transplantation on cardiovascular morbidity and overall mortality compared with continued dialysis, although posttransplantation outcomes may be inferior to normal weight KTRs. However, these studies failed to incorporate diabetes and coronary artery disease as the most important obesity associated comorbidities in the multivariate models of patient and allograft survival. In addition, a high BMI at transplantation has been associated with an increased risk of acute cellular rejections that in turn significantly attenuated the association with inferior allograft survival.

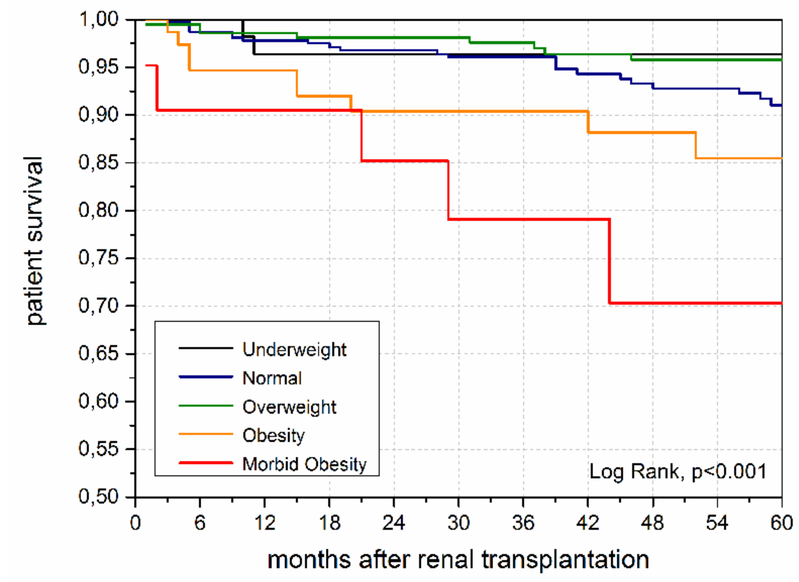
## PATIENTS AND METHODS

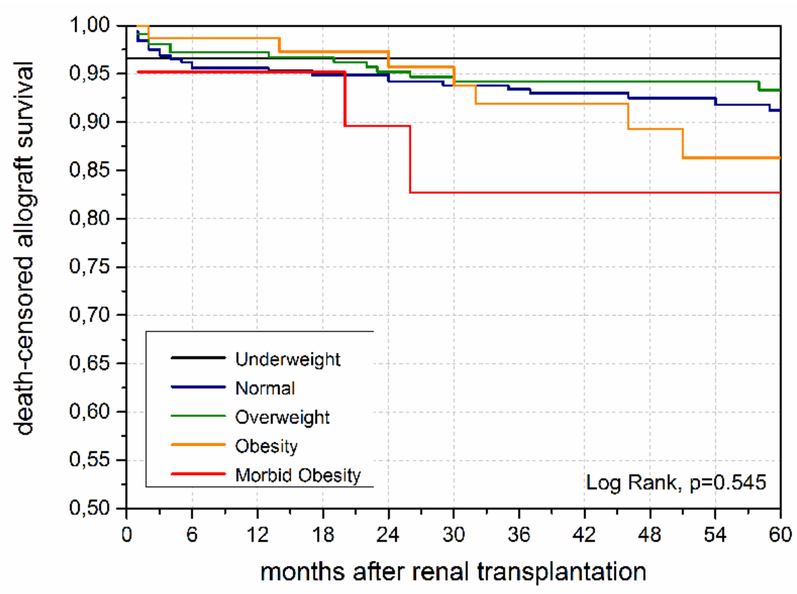
We examined 660 solitary KTRs with regards to their BMI at the time of transplantation and the presence of diabetes-associated comorbidities as diabetes mellitus and coronary artery disease. We attempted to address the following questions: (1) What impact do obesity-related comorbidities have on posttransplantation outcomes? (2) Do obesity-related comorbidities prove useful to identify those obese KTRs at increased risk of adverse outcomes? (3) Are there differences in alloreactivity with regard to obesity? Here, we compared clinical characteristics and outcomes in the different BMI categories with respect to obesity-related comorbidities. Alloreactive T-cells were measured by interferon-gamma Elispot assay.

| | BMI <18.5 (n=29) | BMI 18.5-25 (n=317) | BMI 25-30 (n=217) | BMI 30-35 (n=76) | BMI >35 (n=21) | *P Value* |
|---|---|---|---|---|---|---|
| **Age**, years | 48 (18-74) | 52 (19-77) | 53 (18-76) | 53 (24-72) | 52 (28-78) | *0.653* |
| **Donor age**, years | 49 (11-82) | 54 (11-85) | 54 (13-85) | 55 (12-82) | 52 (23-75) | *0.782* |
| **Male sex**, n (%) | 14 (48) | 205 (65) | 141 (65) | 53 (70) | 9 (43) | *0.077* |
| **Pre-existent diabetes**, n (%) | 2 (7) | 33 (11) | 40 (18) | 26 (35) | 7 (33) | ***<0.001**** |
| **NODAT**, n (%) | 3 (10) | 31 (10) | 30 (14) | 11 (15) | 5 (24) | *0.249* |
| **Coronary artery disease**, n (%) | 2 (7) | 39 (12) | 35 (16) | 15 (20) | 6 (29) | *0.092* |
| **Sepsis**, n (%) | 3 (10) | 27 (9) | 24 (11) | 12 (16) | 4 (19) | *0.264* |
| **Delayed Graf Function**, n (%) | 4 (14) | 74 (23) | 66 (30) | 27 (36) | 7 (33) | ***0.039**** |
| **Acute rejection**, n (%) | 10 (34) | 97 (31) | 80 (37) | 24 (32) | 6 (29) | *0.630* |
| **Surgical complications**, n (%) | 4 (14) | 70 (22) | 45 (21) | 14 (18) | 3 (14) | |
| **Wound healing disturbances**, n (%) | 1 (3) | 14 (4) | 28 (13) | 12 (16) | 6 (29) | ***<0.001**** |
| **Hospital stay duration**, days* | 22 (11-91) | 21 (9-189) | 22 (8-202) | 24 (8-139) | 19 (13-84) | *0.408* |

| | Obesity all (n=97) | Obesity with Diabetes (n=33) | Obesity without Diabetes (n=64) | *P Value* |
|---|---|---|---|---|
| **Delayed Graf Function**, n (%) | 34 (35) | 17 (52) | 17 (27) | ***0.024**** |
| **Acute rejection**, n (%) | 30 (31) | 12 (36) | 18 (28) | *0.488* |
| **Wound healing disturbances**, n (%) | 18 (19) | 9 (27) | 9 (14) | *0.167* |
| **Hospital stay duration**, days | 23 (8-139) | 34 (12-139) | 22 (8-98) | ***0.008**** |
| **Causes of allograft loss**, n (%) | | | | |
| acute rejection | 4 (4) | 2 (6) | 2 (3) | *0.603* |
| fibrosis/atrophy | 3 (3) | 1 (3) | 2 (3) | *1* |
| death with function | 18 (19) | 11 (33) | 7 (11) | ***0.012**** |
| **Causes of death**, n (%) | | | | |
| cardiovascular disease | 2 (2) | 2 (6) | 0 (0) | *0.113* |
| infection | 12 (4) | 6 (18) | 6 (9) | *0.328* |
| other or undetermined | 4 (4) | 3 (9) | 1 (2) | *0.113* |

## RESULTS



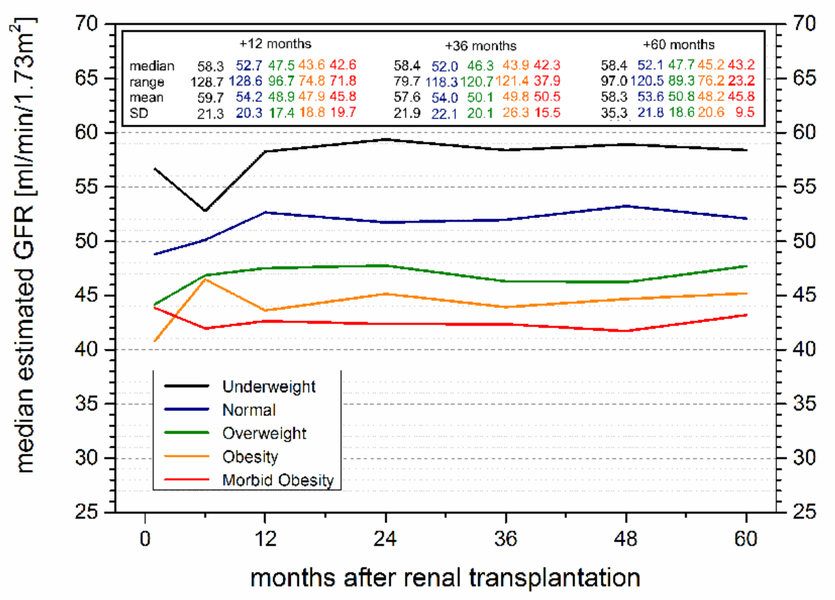
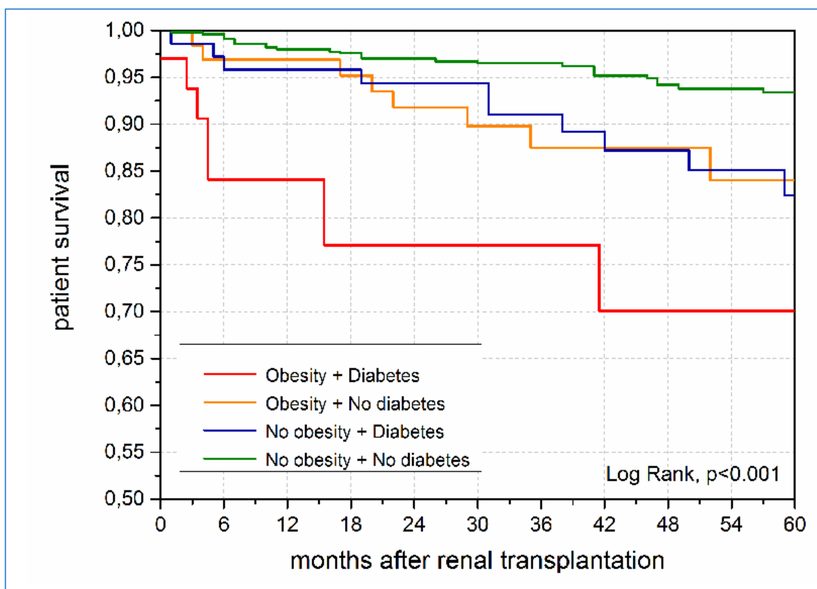
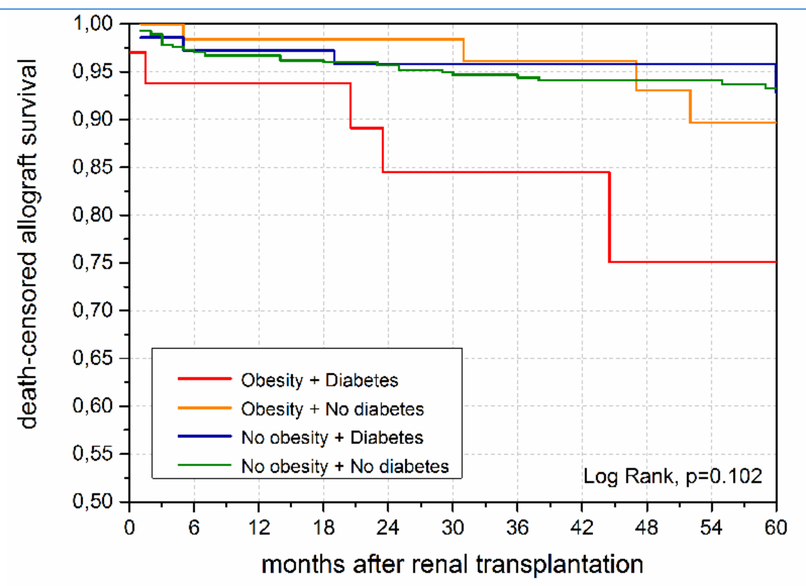




**Figure 1A-C: 1A Kaplan-Meier plot of patient survival.** Significantly lower patient survival in obese and morbid obese KTRs compared to normal-weight KTRs (p<0.001). **1B Kaplan-Meier plot of death-censored allograft survival.** No differences in death-censored allograft survival between all BMI groups (p=0.545). **1C Kidney allograft function in different BMI categories.**



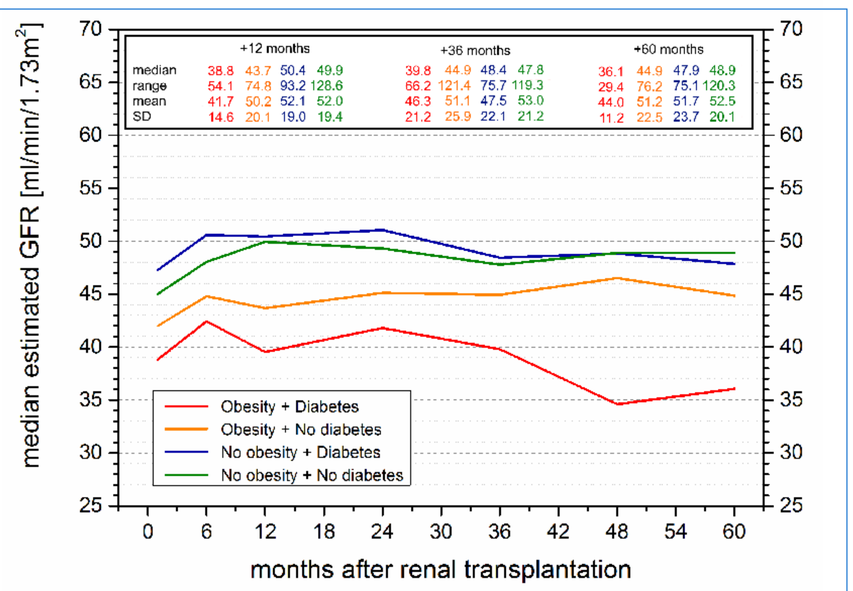




**Figure 2A-C: 2A Kaplan-Meier plot of patient survival.** Lower patient survival in KTRs with obesity plus diabetes (p<0.001). **2B Kaplan-Meier plot of death-censored allograft survival.** Tendency for allograft survival in KTRs with obesity plus diabetes (p=0.102). **2C Kidney allograft function.** Inferior allograft function in obese KTRs plus diabetes starting at +36 months (p<0.05).

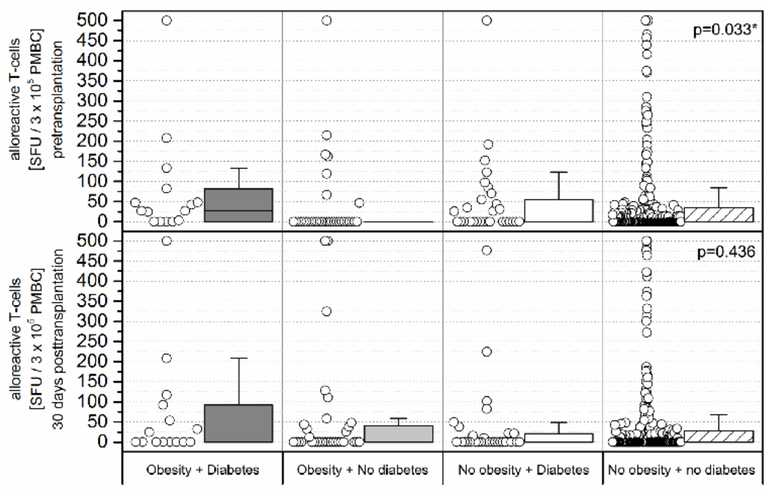



**Figure 3: Significantly higher alloreactive T-cells in obese KTRs with pre-existing diabetes.**

## CONCLUSIONS

1. **Inferior patient survival in obese KTRs limited to those KTRs with diabetes.** Preexisting diabetes may antagonize the beneficial effects of obesity during dialysis, and puts those KTRs at a significantly increased risk of death from infection.
2. **Inferior allograft survival and function in obese KTRs limited to those with diabetes.** The observed worse allograft survival in obese KTRs with diabetes is likely multifactorial and a cumulative effect of obesity and diabetes. The progressive deterioration of allograft function may result from pathologic changes consistent with diabetic nephropathy, obesity-related hyperfiltration and proteinuria, and immunological injury due to high frequencies of alloreactive T-cells.
3. **Increased risk of DGF, wound healing disturbances, and prolonged hospitalization in obese KTRs limited to those with diabetes.** DGF may be caused through a combination of ischemic injury due to advanced vascular calcifications in the presence of diabetes and coronary artery disease, and immunologic injury with higher frequencies of alloreactive T-cells. The observed severe wound healing disturbances most likely is a summation effect of both diabetes and obesity.
4. **Higher incidence of preformed alloreactive T-cells in obese KTRs with diabetes.** Preformed alloreactive T-cells have been suggested to be highly associated with early acute cellular rejection and delayed graft function. These increased frequencies of alloreactive T-cells in obese diabetic KTRs may result from an obesity-related systemic inflammatory state of visceral adipose tissue plus exaggerated inflammatory responses in response to chronic hyperglycemia.

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