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# Does delayed kidney graft function increase the risk of chronic rejection?

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**Abstract** The impact of delayed graft function (DGF) on later renal graft loss due to chronic rejection was studied in a single center using uniform protocol for organ procurement and posttransplant patient care. DGF function was observed in 34 % of 829 consecutive first cadaveric renal transplants in adults and in 47 % of 169 retransplantations ($P < 0.05$). There were no significant differences in graft survival between groups with early graft function (EGF) and DGF, either in first transplantations or retransplantations. The half-life in EGF and DGF groups of first transplants was 12.3 years and 10.5 years, respectively, and of retransplantants was 8.0 years and 6.5 years, respectively. DGF was divided in three subgroups according to the day of onset. If graft function started during the first or second week after transplantation there were no significant differences in long-term graft survival rates compared with EGF. Only in retransplants, if graft function started later than 2 weeks postoperatively, were long-term graft survival rates significantly lower when compared with EGF and the difference persisted if other causes of graft loss except chronic rejection were censored.

**Key words** Chronic rejection · Delayed graft function · Graft outcome

## Introduction

The reports on the impact of delayed graft function (DGF) on later graft outcome has been controversial [3, 5, 6]. Recently DGF has been shown to have an adverse effect on graft outcome at least during the first postoperative year [3, 7]. After the first year, the yearly risk of graft loss due to chronic rejection is about 4 % [4]. Several risk factors may contribute to the original injury of the endothelial cell wall in the renal allograft leading to vascular chronic rejection. Delayed graft function (DGF) can be a sign of some original injury in a renal graft. The aim of this single center study was to investigate whether DGF increases the risk of chronic rejection in cadaveric renal transplants with uniform initial immunosuppression.

## Patients and methods

In Helsinki, between January 1986 and 7 December 1993, 1170 renal transplantations were performed which included 58 (5 %) transplantations in children under 16 years and 79 (6.8 %) living-related transplantations in adults. The study population consists of all 1036 consecutive cadaveric renal transplantations in adults. Two study groups were created. The possible risk of DGF was analyzed for first transplants ($n = 854$) and retransplants ($n = 182$) separately.

Graft function was defined as early (EGF) if no dialysis was needed during the first week and at the same time serum creatinine decreased spontaneously. Fifteen patients with one dialysis during the first week were included in the EGF group because serum creatinine was decreasing rapidly every day and the need for one dialysis was due to fluid overload after the operation. DGF was defined as a need for dialysis during the first week or if serum creatinine failed to decrease spontaneously. In DGF, the onset of graft function was defined as the day of first spontaneous decrease of serum creatinine. Postoperatively, serum creatinine was recorded ev-

**Table 1** Graft survivals in early graft function (EGF) and delayed graft function (DGF) groups for first cadaveric renal transplants and retransplants. Furthermore, DGF is divided in subgroups according to the day of onset

| | Graft survival time | EGF | DGF | Subgroups of DGF | | |
|---|---|---|---|---|---|---|
| | | | | 1–7 days | 8–14 days | > 14 days |
| First transplantation ($n$ = 829) | 3 years | 82 % | 75 % | 73 % | 75 % | 74 % |
| | 6 years | 71 % | 62 % | 57 % | 67 % | 63 % |
| Retransplantation ($n$ = 169) | 3 years | 77 % | 75 % | 86 % | 72 % | 71 % |
| | 6 years | 62 % | 59 % | 78 % | 66 % | 43 % |

**Table 2** Half-lives in years ($T^1/_2$) calculated for the EGF and DGF groups including all causes of graft losses and censoring other causes of graft loss except chronic rejection

| | First transplants | | Retransplants | |
|---|---|---|---|---|
| | $T^1/_2$ | Censored $T^1/_2$ | $T^1/_2$ | Censored $T^1/_2$ |
| EGF | 12.3 | 16.2 | 8.0 | 12.1 |
| DGF | 10.5 | 14.8 | 6.5 | 12.9 |

**Table 3** Half-lives in years in subgroups of DGF including all causes of graft losses and censoring other causes of graft loss except chronic rejection

| DGF | First transplants | | Retransplants | |
|---|---|---|---|---|
| | $T^1/_2$ | Censored $T^1/_2$ | $T^1/_2$ | Censored $T^1/_2$ |
| Onset 1–7 days | 8.2 | 10.7 | 10.3 | 13.0 |
| Onset 8–14 days | 10.9 | 12.1 | 6.2 | 17.9 |
| Onset > 14 days | 13.5 | 16.0 | 3.9 | 5.4 |

ery day during the 3–4 week stay at the transplantation unit. DGF was divided in three groups according to the onset of graft function: 1–7 days, 8–14 days, and over 14 days, postoperatively. Diagnosis of chronic rejection was based on clinical criteria. Graft loss due to chronic rejection was defined as a gradual but progressive deterioration of graft function leading to dialysis in the absence of other specific causes. Biopsies were not available from all grafts, but if there was no biopsy other possible causes of late graft dysfunction were excluded by clinical investigations.

Since 1986 our immunosuppressive protocol has been the same. All cadaveric renal transplant patients have received triple therapy with cyclosporine, azathioprine, and methylprednisolone. Immunologically high risk patients (previous transplant lost due to immunological reasons and high panel-reactive antibodies) have, furthermore, received polyclonal or monoclonal antibodies for 7–10 days as induction therapy. Oral cyclosporine was started before the operation, 5 mg/kg body weight, and it continued afterwards, 10 mg/kg per day in two doses. Cyclosporine was given independently of primary graft function and the dose was adjusted to trough blood levels measured at least twice per week. All grafts were from heart-beating donors and the organs were procured according to uniform protocol.

The risk of graft loss in chronic rejection was compared between the groups of patients with EGF and DGF. The graft survival was calculated using an actuarial life-table method and the differences between groups by the log-rank method. To study the long-term effect half-life was calculated. The estimation of half-life was based on least square exponential curve fitting of survival between 1 and 6 years posttransplant. Half-life is the estimated time needed for 50 % of the grafts functioning at 1 year after transplantation to fail.

## Results

The number of grafts which never function in first transplants and in retransplants were 2.9 % (25/854) and 7 % (13/182), respectively, and these grafts were excluded from the final study groups. DGF was recognised in 34 % (281/829) of first transplants and in 43 % (79/169) of retransplants ($P < 0.01$). Distribution of transplants in the three subgroups of DGF, i.e., onset of graft function during the first week, second week and after 2 weeks, were 44 % (124), 35 % (98), and 21 % of all 281 first grafts with DGF, respectively, and 29 % (23), 34 % (27), and 37 % (29) of all 79 retransplants with DGF, respectively. The 3-year and 6-year graft survival (GS) in EGF and DGF and, furthermore, in the subgroups of DGF is presented in Table 1. The difference in GS between first transplants with EGF and DGF was not significant (log-rank test, chi-squared = 4.37, $P < 0.1$) and neither in retransplants (chi-squared = 0.364, NS). In first transplants GS did not differ significantly in DGF subgroups. In retransplants GS rates decreased in DGF subgroups with increasing time of onset (Table 1), but the difference was not significant in any subgroups compared with EGF.

The calculated half-life after 1 year was slightly higher in the grafts with early function than in the grafts with DGF (Table 2), both in first and retransplants. If all other causes of graft loss but chronic rejection were censored, half-life for first grafts with DGF function was 1.4 years shorter and for retransplants with DGF half-life was 0.8 years longer compared to the grafts with early function (Table 2).

For the grafts functioning at 1 year, later graft survival rates did not differ between EGF and the DGF except GS in retransplants with EGF was significantly higher compared to the group of DGF with onset after 2 weeks (log-rank test, chi-squared = 5.67 $P < 0.05$) including all causes of graft losses and also censoring other causes except chronic rejection (chi-squared = 5.94, $P < 0.05$). Half-lives of the subgroups of DGF are presented in Table 3. In first transplants, this more close analysis showed the shortest half-life in the group of DGF with onset of function during first week. In first transplants, there was no correlation in half-lives or in GS rates after the first year including all graft losses or only graft losses due to chronic rejection. In retransplants, half-life correlated inversely with increasing

time of onset including all grafts and also if other causes except chronic rejection were censored. In retransplants, GS rates after the first year were significantly lower in the group of DGF with onset after 2 weeks compared with EGF both if all causes of graft loss were included and also if other causes except chronic rejection were censored.

## Discussion

In this study population, frequency of DGF (34 %–47 %) was high. EGF is usually defined as no need for dialysis. Our criteria also included the demand for spontaneously decreasing serum creatinine which increases the frequency of DGF to some extent. DGF occurred significantly more often after retransplant than after first graft which might be due to some immunological influence on graft function in retransplants.

We have shown earlier that, in our patient population, acute allograft rejection is no longer a risk for later graft outcome at least in first cadaveric renal transplants. This controversial result, compared with many other recent studies [1, 2], might be in part explained by our genetically homogenous population (all patients ethnically Finns) and low frequency of acute rejections. Furthermore, acute rejections under initial triple therapy have been mild and reversible. However, the risk of graft loss due to chronic rejection is about 4 % every year [4]. DGF can be a sign of some initial endothelial cell damage in the graft with a subsequent response to injury leading to intimal proliferation and chronic vascular rejection.

Long-term consequences of DGF, excluding the early graft losses, have seldom been investigated. Our interest was to analyze the impact of DGF on half-lives of the grafts. In first transplants, graft survival curves did not differ after the first year posttransplant in EGF and DGF groups and the half-lives did not correlate with the onset of graft function. Our results do not confirm the negative effect of DGF on later graft outcome. We found that only the subgroup of retransplants with onset of function after 2 weeks had a significantly higher risk of losing a graft compared with EGF.

Aetiology of DGF is certainly multifactorial. We can only postulate that such factors which have an impact on DGF causing the increased risk of later graft loss are minimised in our program. In our center many possible causes of DGF are minimised. HLA matching is used for donor selection. The quality of organs is optimized with strict donor criteria and the same transplant team is responsible in the whole country for the organ harvesting program. Moreover, it is interesting that although we started the cyclosporine before kidney transplantation and it was continued irrespective of early graft function, there were no significant differences in long-term graft survival rates or in the half-lives between EGF and DGF groups in first transplants. What the consequence of our cyclosporine policy is to the low acute rejection frequency is not known.

In conclusion, we could not confirm the impact of DGF on later graft outcome on first transplants. Retransplants had more DGF compared with first transplants. Only retransplants with the onset of graft function later than 2 weeks postoperatively showed poorer outcome compared with EGF.

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