



METABOLIC FACTORS HAVE A MAJOR IMPACT ON KIDNEY ALLOGRAFT SURVIVAL

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## Abstract

**Background:** At the present time, late graft loss is the major cause of kidney failure after transplantation. However, the influence of metabolic factors on this process is ill-defined.

**Methods.** To identify the impact of lipid metabolism, glucose metabolism, and blood pressure and their prognostic value for graft survival, data for all recipients of a kidney allograft with a potential graft survival of >15 years and a minimum graft survival of 1 month were analyzed retrospectively. Recipients of kidney grafts functioning more than 15 years (n=32) were compared with those with a graft function of less than 10 years (n=152, controls) and evaluated in a multivariate analysis.

**Results.** Low levels of serum cholesterol, triglycerides, and glucose, before and after transplantation, were accompanied by a prolonged graft survival. Prognostic factors for early graft failure included serum

triglycerides >300 mg/dl, cholesterol >250 mg/dl before transplantation, serum creatinine >4.0 mg/dl 1 month after transplantation, and donor age above 45 or less than 10 years. Additionally, systolic and, particularly, diastolic blood pressure was lower in the group with a prolonged graft function as compared with controls immediately before and after transplantation. In addition, the incidence of primary graft function was lower and the incidence of acute rejection episodes higher in controls. Cold and warm ischemic time, body mass index, recipient age, and gender did not differ significantly.

Conclusions. Our data suggest that metabolic parameters play an important role in the process of late graft loss after kidney transplantation.

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Despite a 1-year graft survival of 80-90% in most transplant centers, renal transplantation has not reached its potential as a permanent treatment of chronic renal failure (1-3). Chronic rejection is the predominant reason for late graft loss (2, 3). Although the introduction of cyclosporine has improved short-term graft survival, the rate of attrition did not change over the long term (1, 2, 4). The rate of attrition observed in cyclosporine-treated patients closely mirrors that of the chronic decline common to conventionally treated patients (5). The factors influencing this process are ill-defined. The histological features observed in these grafts are fibrosis, intimal proliferation, and vascular occlusion (6). These features have many resemblances to arteriosclerosis (2). Because metabolic parameters-such as serum lipid and glucose levels-and systemic blood pressure are important contributors to the development of arteriosclerosis, it has been hypothesized that they may also affect long-term allograft survival (6-8).

The aim of this retrospective study was to analyze the predictive value of metabolic factors and blood pressure for long-term graft survival.

#### PATIENTS AND METHODS

To evaluate predictors of late graft failure, we focused on transplant recipients with a potential graft survival of more than 15 years. Between 1972 and 1980, 347 patients who were over 18 years of age received a cadaver kidney transplant at the University Hospital of Essen. Patients with missing pretransplant data were excluded (n=35). To eliminate grafts that never functioned, hyperacute or accelerated rejections, and surgical problems, only those patients with a graft survival of more than 1

month were included in the study (n=184). The 1-year graft and patient survival rate at our center was 49%, better than average at that time (9).

All patients were treated with azathioprine (1-2 mg/kg body weight, to achieve white blood cell counts <5000/ $\mu$ l) and prednisolone (500 mg/day initially, slowly tapered to 10 mg/day). (After the introduction of cyclosporine, four patients in the control group and one patient in the prolonged graft function group were converted from azathioprine to cyclosporine.) For the analysis, patients were divided into two groups: patients with a graft function of more than 15 years (n=32) and those patients (controls, n=152) who lost their grafts between 1 month and 10 years after transplantation. In the control group, the average graft survival time was  $2.6 \pm 0.2$  years (range, 1 month to 9.5 years). There were no differences in age and gender of recipients and in cold and warm ischemic time between the two groups (Table 1). The duration of dialysis before transplantation was somewhat shorter and patients with panel-reactive antibodies were more common in the control group, but these differences were not statistically significant. For organ preservation, Euro-Collins solution was predominantly used within both groups. It has been well-documented that HLA mismatches influence long-term graft outcome. The strongest association is found with HLA-DR antigen mismatches (3, 5, 10). At the time of transplantation of the patients evaluated in this study, however, HLA typing was much less developed, and HLA-DR antigen subtypes were not defined; therefore, it was not possible to evaluate the impact of this factor on long-term graft survival.

Table 1

	Prolonged graft function (n=32)	Controls (n=152)	P
Age in years (range)	38 (20–51)	35 (18–59)	NS
Gender	16 female and 16 male	65 female and 87 male	NS
Duration of dialysis before Tx (years)	$3.1 \pm 0.2$	$2.6 \pm 0.15$	<0.05
Patients with panel-reactive antibodies >5%	n=1	n=4	NS
Cold ischemia (hr)	$17.3 \pm 1.4$	$18.5 \pm 0.6$	NS
Warm ischemia (min) <sup>b</sup>	$34.9 \pm 2.6$	$32.2 \pm 0.9$	NS
Euro-Collins perfusion (%)	91	90	NS

<sup>a</sup> There were no significant differences between the two groups, regarding age and gender, duration of dialysis before transplantation, panel-reactive antibodies, ischemia times, and perfusion solution (NS, not statistically significant).

<sup>b</sup> Second warm ischemia.

Table 1. General description of patients<sup>a</sup>

The following variables with a possible influence on long-term graft survival were analyzed: metabolic parameters (serum cholesterol, triglyceride and glucose levels, systemic blood pressure, and body mass

index[BMI <sup>†</sup>]), peritransplant variables (donor age), functional factors (serum creatinine levels and primary graft function), and alloantigen-dependent factors (retransplantation and acute rejection episodes).

Graft survival was calculated according to the Kaplan-Meier method, considering data of patients who died with a functioning graft as censored data. First, a multivariate analysis was performed to identify risk factors of late graft loss. Results are presented as average  $\pm$  SEM. After the risk factors were identified, a Cox analysis (11) was performed in all patients with a possible graft survival of more than 15 years, an actual graft survival of more than 1 month, and an age over 18 years at the time of transplantation to evaluate the independent prognostic value of these risk factors. Further regression analysis was performed to evaluate the correlation of these values to graft survival.

## RESULTS

Metabolic factors. Total serum cholesterol, triglyceride, and fasting blood glucose levels were significantly lower in patients with prolonged graft survival before transplantation and throughout the follow-up period, as compared with controls (Table 2). The risk of graft deterioration was also significantly increased in patients with higher systolic and especially with higher diastolic blood pressure values: diastolic blood pressure was significantly elevated in the control group compared with the prolonged graft function group throughout the whole follow-up period. Systolic blood pressures paralleled these higher diastolic values.

Table 2

	Before transplantation			5 years after transplantation		
	Prolonged graft function (n=32)	Controls (n=152)	P	Prolonged graft function (n=32)	Controls (n=104)	P
Serum cholesterol (mg/dl)	188 $\pm$ 7	217 $\pm$ 13	<0.01	229 $\pm$ 8.5	248 $\pm$ 215	<0.05
Serum triglycerides (mg/dl)	145 $\pm$ 21	310 $\pm$ 51	<0.01	148 $\pm$ 24.4	201 $\pm$ 23	<0.05
Fasting blood glucose (mg/dl)	74 $\pm$ 3	85 $\pm$ 5	<0.01	79 $\pm$ 4.5	80 $\pm$ 4.8	<0.05
Systolic blood pressure (mmHg)	144 $\pm$ 7	148 $\pm$ 3	<0.05	135 $\pm$ 3.6	138 $\pm$ 4.2	<0.05
Diastolic blood pressure (mmHg)	84 $\pm$ 3	88 $\pm$ 1.7	<0.01	78 $\pm$ 1.2	83 $\pm$ 3.7	<0.01
Serum creatinine (mg/dl)	-	-	-	1.2 $\pm$ 0.04	2.5 $\pm$ 0.2	<0.01
BMI (kg/m <sup>2</sup> )	20.52 $\pm$ 0.42	20.4 $\pm$ 0.4	NS	22.3 $\pm$ 0.4	22.6 $\pm$ 0.2	NS

<sup>†</sup> Cholesterol, triglycerides, glucose, systemic blood pressure and creatinine increased during the follow-up, and were significantly higher in controls than in the prolonged graft function group. There were no significant differences regarding body mass index between the two groups. NS, not significant.

Table 2. Metabolic parameters before and after transplantation<sup>a</sup>

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To eliminate the possible bias of acute rejection and delayed graft function, we analyzed patients with a primary graft function and with only one or with no acute rejection episode. In this subgroup, serum cholesterol (179±8 mg/dl vs. 221±18 mg/dl; P<0.05) and triglycerides (131±11 mg/dl vs. 244±16 mg/dl; P<0.01) before transplantation were also significantly lower in the group with prolonged graft survival (n=13) as compared with controls (n=50). However, although systemic blood pressure (150±12/87±5 mmHg vs. 151±4/88±2 mmHg) and fasting blood glucose levels (78±4 mg/dl vs. 79±4 mg/dl) were also lower in the prolonged graft function group, these differences were not statistically significant.

Cox's regression analysis of these metabolic parameters before transplantation identified cholesterol (P=0.045) and triglyceride levels (P=0.02) as independent prognostic determinants of late graft failure, whereas blood glucose and systemic blood pressure were removed from the Cox model as variables not significantly explanatory for graft survival time. Serum cholesterol >250 mg/dl and serum triglyceride >300 mg/dl before transplantation were accompanied by shorter graft survival ([Figs. 1 and 2](#)). Patients with cholesterol of more than 250 mg/dl and triglycerides >300 mg/dl had an average graft survival of 4±1.5 years, whereas those with lower pretransplant serum lipids reached 8±0.8 years (P<0.01). Linear regression analysis demonstrated that serum triglyceride levels correlated (r=-0.34) even more strongly with graft survival (P=0.0036) than did cholesterol levels (r=-0.32, P=0.0095). In contrast, fasting blood glucose and systemic blood pressure values did not correlate significantly with graft survival.

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Figure 1

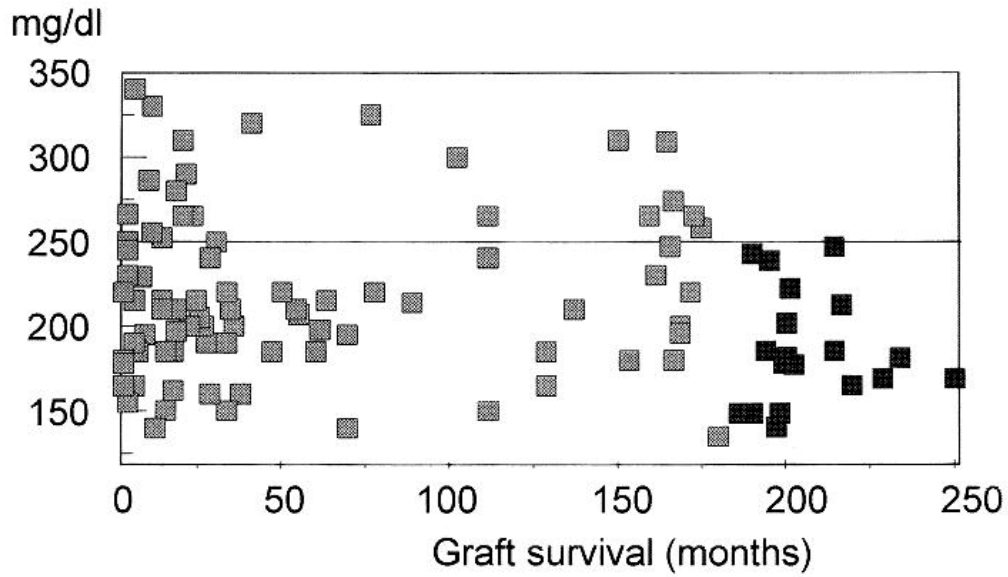


Figure 1. Serum cholesterol. Serum cholesterol levels before transplantation were significantly higher in the control group. Cholesterol levels correlated with graft survival, and serum cholesterol >250 mg/dl was accompanied by short graft survival. [dotted square], Controls; [black small square], prolonged graft function.

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Figure 2

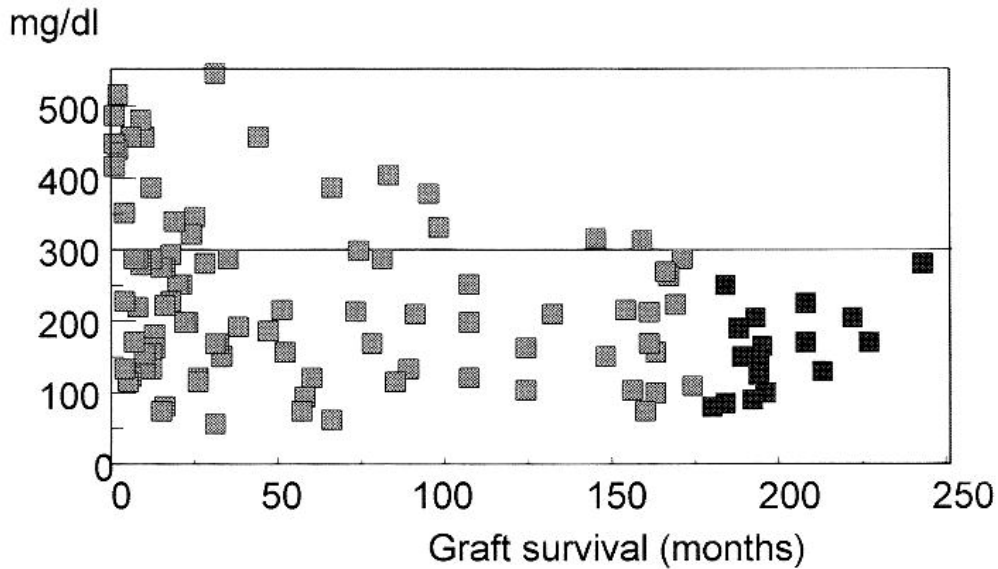


Figure 2. Serum triglycerides. Serum triglyceride levels before transplantation were significantly elevated in the control group. Triglyceride levels correlated with graft survival even more strongly than did cholesterol levels. Serum triglycerides >300 mg/dl were accompanied by a shorter graft survival. [dotted square], Controls; [black small square], prolonged graft function.

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Surprisingly, there was no difference between the groups regarding BMI before transplantation. Average BMI increased after transplantation, and in the long run, this increase was slightly more pronounced in the prolonged graft function group, but the differences were not significant.

Peritransplant variables. In general, a donor age <10 or >45 years was accompanied by shortened graft survival; survival of these patients was  $3.5 \pm 0.4$  years versus  $7.2 \pm 1.6$  years ( $P < 0.01$ ) in patients whose donors were between 10 and 45 years of age. There was a tendency toward a higher average donor age in controls as compared with patients with prolonged graft function ( $26.7 \pm 5.3$  vs.  $23.5 \pm 4.5$  years), but this difference was not statistically significant.

The average age of recipients, distribution of gender between recipients, and duration of dialysis before transplantation did not differ between the groups ([Table 1](#)).

An assessment of engraftment data shows that there were only minor differences regarding cold and warm ischemic time between the two groups. ([Table 1](#)).

Functional and alloantigen-dependent parameters. Primary graft function-defined as less than two instances of dialysis within the first 7 days after transplantation-strongly correlated with allograft survival: primary graft function was observed in 19 of 32 grafts with prolonged graft function (59.4%) and in 53 of 152 patients (34.9%) in the control group( $P<0.01$ ).

The risk of graft deterioration was higher among patients with acute rejection: a total of 40.6% of patients had at least one acute rejection episode in the prolonged graft function group versus 67.7% in the control group ( $P<0.01$ ). Nine of the 32 patients (28.1%) with prolonged graft function had one, 4 of them (12.5%) had two, and none of them had three acute rejection episodes. In the control group, 6 of 152 (39.5%) had one, 31(20.4%) had two, and 12 patients (7.8%) had three acute rejection episodes.

In general, patients who received their first transplant had a significantly longer graft survival time ( $6.5\pm 0.5$  years) than did patients receiving their second or third graft ( $4.5\pm 1.5$  years; $P<0.01$ ).

Creatinine levels were significantly lower in the prolonged graft function group as compared with controls throughout the whole follow-up period. The Cox analysis identified serum creatinine levels 1 month after transplantation as the most significant ( $P=0.001$ ) predictor of late graft failure. Serum creatinine  $>4$  mg/dl 1 month after transplantation was accompanied by shorter allograft survival. If serum creatinine was  $<4$  mg/dl 1 month after engraftment, average graft survival was  $6.7\pm 0.5$  years, as compared with  $4.1\pm 1$  years if creatinine was  $>4$  mg/dl ( $P<0.01$ )([Fig. 3](#)). Regression analysis demonstrated that serum creatinine levels were significantly correlated ( $r=-0.36$ ) with graft survival ( $P<0.0001$ ).

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Figure 3



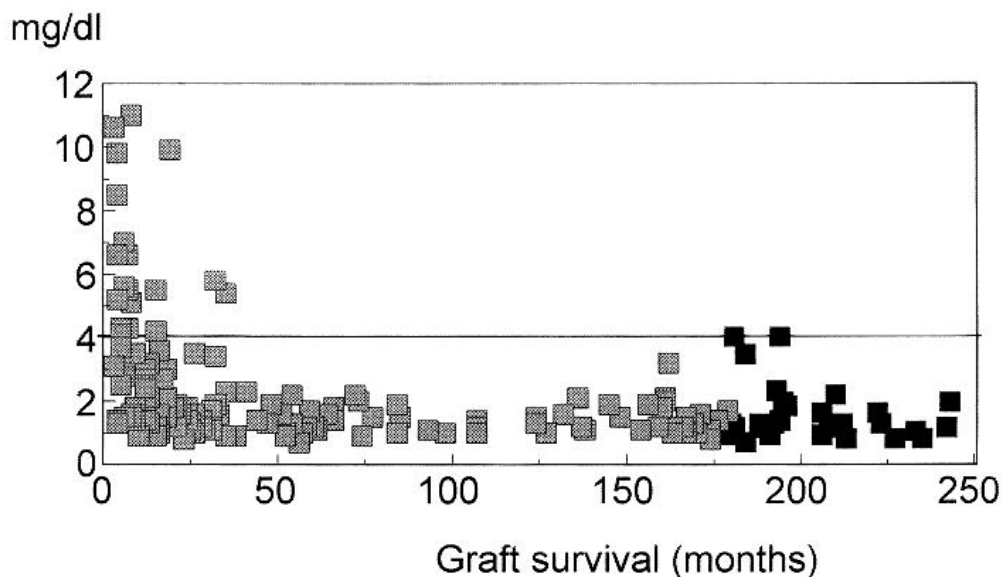


Figure 3. Serum creatinine. Serum creatinine 1 month after transplantation was significantly higher in the control group. The strongest correlation of graft survival was found with serum creatinine. Creatinine levels >4 mg/dl were accompanied by an increased risk of graft failure. [dotted square], Controls:[black small square], prolonged graft function.

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## DISCUSSION

Chronic rejection is responsible for a majority of the late graft losses after renal transplantation. The participation of metabolic factors such as hyperlipidemia, diabetes mellitus, and hypertension within process has recently gained attention [\(6\)](#).

Some observers noted a correlation between hyperinsulinemia, resistance to insulin action, obesity, high arterial blood pressure, and especially high serum lipid values and the risk of long-term graft failure in renal transplant recipients [\(1, 8\)](#). Our data suggest that serum lipids before and after transplantation correlate with long-term graft survival. Serum cholesterol >250 mg/dl and serum triglycerides >300 mg/dl were associated with shorter allograft survival. The correlation was stronger in the case of triglycerides ( $r=-0.34$ ) as compared with cholesterol( $r=-0.32$ ), but the latter was significant as well. The lower pretransplant glucose levels in the group with prolonged graft function indicate a certain role for glucose in the process. However, as this correlation was statistically not significant in the Cox regression analysis, glucose may not be an independent predictor but rather the consequence of otherwise altered metabolic

parameters. Our data support the hypothesis that arteriosclerotic processes play an important role in the development of late graft failure [\(6\)](#).

Several investigators [\(2, 4, 12, 13\)](#) emphasized the importance of systemic blood pressure for graft survival. In our analysis, low systolic and, especially, diastolic blood pressures before as well as after transplantation were also accompanied by prolonged graft function. A possible explanation for the pathogenic role of systemic hypertension might result from an accelerated process of arteriosclerosis of renal vessels, with hypoxia-induced sclerosis of the glomeruli downstream [\(13, 14\)](#).

Peritransplant variables. Before 1975, a strong long-term effect of cold ischemic time was noted [\(15, 16\)](#). After 1975, the effect of cold ischemia diminished [\(16\)](#). Ineffective kidney preservation methods before 1975 may serve as an explanation for this change [\(16\)](#). An association between conservation solution, cold ischemic times, and graft survival was first noted after the introduction of conservation solutions. In our analysis, only a few patients received transplants before 1975, and the solution used for organ preservation was predominantly Euro-Collins solution [\(Table 1\)](#). Therefore, the numbers may be too small to differentiate between the types of organ preservation used.

Duration of dialysis before transplantation was similar in both groups, indicating that this factor had no influence on graft outcome. This assumption is supported by the reports of Opelz [\(5\)](#), who observed no influence of type or duration of dialysis upon graft survival.

It has been suggested that higher donor [\(3, 5, 8, 17\)](#), but not recipient [\(3, 5, 18\)](#), age has a negative influence on graft survival. In our patients, differences between the two groups did not reach statistical significance. Donor age was somewhat lower in the prolonged graft function group, and grafts from donors younger than 10 or older than 45 years of age had a poor long-term graft survival. Cecka reported that kidneys from pediatric donors, as well as from donors older than 55 years, were associated with a shortened half-life of kidney transplants [\(3, 19\)](#). Brenner et al. [\(20\)](#) also reported a higher graft loss in cases of very younger or very old donors. He attributed his findings to the lower functional capacity of these kidneys.

Functional parameters and alloantigen-dependent variables. Our results demonstrate a strong correlation between elevated serum creatinine levels and reduced graft survival, with a high predictive value of an initial serum creatinine (>4 mg/dl). This is supported by results from a variety of other investigators. Almost all investigators studying the causes of late graft loss found a strong relationship between initial serum creatinine levels and long-term graft survival. Kahan et al. [\(12\)](#) reported that serum creatinine at 1 month after transplantation is a good prognostic index for long-term graft outcome. In this respect,

creatinine may serve as an indicator of overall kidney damage. Independent of the reason-acute rejection, surgical trauma, or infection-once a kidney is impaired, creatinine rises [\(21\)](#). Thus, this observation may be interpreted to favor the hyperfiltration theory, as has been demonstrated in animal experiments [\(21\)](#).

It is generally accepted that patients who have already rejected a previous graft are at a higher immunologic risk of rejecting another one [\(12\)](#). Thus, it was not surprising that first transplants had a much better survival rate than second transplants, and that third transplants had the worst survival rate in our analysis.

The impact of primary graft function on graft outcome is not fully understood. However, a number of authors [\(11, 12, 23\)](#) have suggested a negative influence on long-term graft survival. Our observations support these observations, as delayed graft function was significantly more frequent in our controls.

The number of acute rejection episodes is a significant, independent risk factor for reduced graft survival [\(11, 23-25\)](#). In the present study, 67.7% of patients in the control group had at least one acute rejection episode, as compared with 40.6% in the prolonged graft function group.

In conclusion, apart from antigen-dependent risk factors, metabolic factors such as high serum lipid levels, as well as high blood pressure, are important contributors to graft loss after kidney transplantation. Serum creatinine >4 mg/dl after transplantation, triglycerides >300 mg/dl, and cholesterol >250 mg/dl before transplantation are predictive values of early graft failure.

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