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Kidney transplantation: Studies on donor risk factors and mycophenolate mofetil

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Author's contribution:

I. The author collected data, performed statistical analyses and was main person in writing the manuscript
II. The author collected data, performed statistical analyses and was main person in writing the manuscript
III. The author collected data, participated in analyses of data and writing the manuscript
IV. The author designed study, collected data, assisted in re-evaluation of the biopsies, performed statistical analyses and was main person in writing the manuscript

ABBREVIATIONS

AE	adverse event
ALAT	serum alanine transferase
AUC	area under the curve
AZA	azathioprine
BMI	body mass index
CADI	chronic allograft damage index
CIT	cold ischemia time
CMV	cytomegalovirus
CyA	cyclosporine
DGF	delayed graft function
ECD	expanded criteria donors
GFR	glomerular filtration rate
GS	glomerulosclerosis
HLA	human leukocyte antigen
MMF	mycophelolate mofetil
MPA	mycophenolic acid
MP	methylprednisolone
TAC	tacrolimus
UK	United Kingdom
UNOS	United Network for Organ Sharing
US	United States

1. INTRODUCTION

Kidney transplantation is the best form of treatment for most patients with end-stage kidney disease, as it improves quality of life, prolonges survival, and is cost-effective (Knoll, 2008).

Shortage of donor organs is one of the biggest obstacles preventing expansion of transplantation activity. With the increasing incidence of end-stage kidney disease, the number of patients waiting for kidney transplantation is escalating world-wide generating the need to expand the donor organ pool (Port, 2003). Different strategies have been attempted to satisfy the demand: live donor kidney transplants, improving consent rates for deceased donor organ procurement, provision of "opting out" (presumed consent) systems, increasing donation after cardiac death, using extended-criteria donors and reducing transplant losses (Shrestha, 2009). Due to the dearth of optimal organ donors, there has emerged a trend to relax donor criteria and to increasingly accept lower quality or "marginal donors". Therefore, it is imperative, to examine which donor factors are associated with subsequent risks for graft loss and which can be accepted for donation and transplantation in special recipient groups.

Many donor factors, donor age being the most important, are known to affect kidney transplantation outcome and have been used in different donor assessment systems (Nyberg, 2001; Rao, 2009). Nevertheless, one can not decide the suitability of a kidney for transplantation based on donor age alone, as many kidneys from older donors reveal no significant pathology in biopsies and have been shown to have a graft survival comparable to kidneys from younger donors (Escofet, 2003; Nghiem, 1993). Medical history of the donor can provide valuable additional information, which has been clearly underutilized in donor assessment.

It remains uncertain what is the best way to determine whether a kidney from a marginal donor is of sufficient quality to ensure an opportunity for long-term graft survival for the recipient. Besides clinical parameters, donor baseline biopsies have been used to assess the suitability of a donor organ, particularly of older donors. In kidney allografts, it has been demonstrated that incipient histological changes, can either individually (Nicholson, 1999) or in combination (Kasiske, 1991; Isoniemi, 1992; Seron, 1997), predict kidney allograft dysfunction in future. What remains open, however, is how donor clinical risk factors and adverse histopathology of the donor kidney are associated. Some proposals for morphologic donor quality criteria have been made based on a rather small number of patients (Gaber, 1995) and have to be therefore definitely assessed in a larger study population.

Chronic Allograft Damage Index (CADI) is the sum of the scores of six histologic findings (interstitial inflammation, tubular atrophy, vascular intimal proliferation, interstitial fibrosis, mesangial matrix increase and glomerulosclerosis), which have been shown to predict long-term graft outcome in post-transplantation kidney allograft biopsies (Isoniemi, 1992). In donor biopsies,

however, the value of the CADI score for predicting kidney allograft outcome has not been thoroughly studied.

Although one-year graft survival in kidney transplantation has improved substantially during last decades, only modest improvements have been observed in some studies on long-term graft survival rates (Cecka, 2001; Marcen, 2009). Overall gain in graft survival has been observed principally owing to fewer cases of acute rejections, which is the result of progress in immunosuppressive drugs and treatment schedules. There is, however, no significant improvement in other leading causes of graft loss – chronic allograft dysfunction and premature death with functioning graft (Schweitzer, 1991; El-Zoghby, 2009). It indicates that more attention and research should be focused to their mechanisms. Several nonimmunological factors have been suggested to contribute to later graft failure, *e.g.* high donor age, cardiovascular risk factors, nephrotoxic immunosuppressants, early graft dysfunction etc. Premature death with functioning graft is also known to be associated with cardiovascular risk factors and increased risk for infections and malignant diseases (Salmela, 2007).

Triple immunosuppression consisting of a calcineurin inhibitor, an antiproliferative agent and steroids has been the mainstay of kidney transplantation programmes during the last decades. After studies confirming a more potent effect of mycophelolate mofetil (MMF) than azathioprine (AZA) in reducing acute rejection risk (Pichlmayr, 1995; Keown, 1996), MMF has progressively replaced AZA as an adjunct antiproliferative agent in most transplant programmes. Significant benefits for long-term kidney transplant survival, however, have not been definitely demonstrated and need therefore further confirmation. After becoming available in Estonia in 1996, MMF was first used as primary therapy in highly immunized patients or as rescue therapy after severe acute rejections.

It is known from earlier reports that rejection rate increased dramatically in those CyA-AZA-steroid triple immunosuppression patients who had to discontinue taking azathioprine early in the post transplant period (Salmela, 2004). Similar intolerance as with AZA has been observed in patients taking MMF (Pelletier, 2003; Knoll, 2003), which may place a transplanted patient at higher immunological risk and lead to worse prognosis.

The purpose of present work was to assess the efficacy and adverse event profile of MMF therapy, but also to investigate risk factors for kidney transplantation outcome and possibilies for donor quality assessment.

2. REVIEW OF THE LITERATURE

2.1 Immunosuppression with mycophenolate mofetil (MMF)

2.1.1 Efficacy of MMF

MMF is an immunosuppressive drug, which inhibits T and B cell proliferation by blocking the production of guanosine nucleotides required for DNA synthesis. MMF has shown significant efficacy in reducing the incidence of acute rejection by approximately 50% compared with AZA in randomised controlled trials, involving nearly 1500 patients with kidney transplant (Pichlmayr, 1995; Sollinger, 1995). Whereas MMF improved patient and graft survival rates in cardiac transplantation, significant benefits for kidney graft survival were not evident after one year (Halloran, 1997) or three years (Mathew, 1998). Paired kidney analysis, carried out in the UK by Shah et al., found no difference in graft survival between MMF and AZA treated patients (Shah, 2006). There is some evidence, however, of a modest survival advantage with MMF therapy over placebo after 3 years (Vanrenterghem, 1999) and over AZA containing treatment after 4 years (Ojo, 2000). The results are more controversial in the case of elderly recipients, who are more susceptible to infectious complications and show considerably lower rates of rejection. Some studies have even suggested worse outcome in elderly recipients with MMF treatment due to over-immunosuppression and opportunistic infections (Johnson, 2002), while others have proved no increased risk of death with MMF compared to AZA (Meier-Kriesche, 2004).

2.1.2 MMF as rescue therapy

There are very few data available on switching or rescue therapy with MMF after acute rejection episode. MMF has been used instead of intravenous corticosteroids in the treatment of acute refractory rejection, with less treatment failures and even better graft survival (Danovitch, 1996). Although MMF has proved to be more effective than AZA in preventing subsequent rejections after first acute rejection episode (Pescovitz, 2001), it is unclear whether these benefits also ensure a better graft survival. Preliminary data indicate that MMF may be effective in salvaging kidney allografts with refractory rejection (Morris-Stiff, 1998; Tomlanovich, 1996).

2.1.3 MMF intolerance

2.1.3.1 Safety of MMF

MMF is generally a well-tolerated non-nephrotoxic drug which does not cause abnormalities in the lipid profile. The most often reported adverse events are gastrointestinal and hematological side-effects (Mele, 2000). Gastrointestinal symptoms are typically mild, such as nausea, vomiting, and diarrhea. During the first posttransplant year, the incidence of diarrhea, but also more serious gastrointestinal complications (gastritis, gastrointestinal hemorrhage), is reported to be twice as high in patients receiving MMF than in those receiving AZA (Keown, 1996). Adverse events are more common in patients treated with MMF 3 g/day compared to patients receiving 2 g/day suggesting a dose-dependent effect (Pichlmayr, 1995). Generally the symptoms resolve with a reduction in total daily dosage. Evaluation of the tolerability profile of MMF is confounded by the high rate of adverse events that occur with concomitantly administered immunosuppressive agents (Bardsley-Elliot, 1999). The adverse events mostly attributed to MMF may also be related to other reasons or to the overall level of immunosuppression. In a European study for example, diarrhoea was noted with the same frequency in the MMF and placebo groups (Pichlmayr, 1995).

Myelosuppression has been reported from large randomized MMF trials with a frequency of 7–35%, leukopenia being the most frequent finding. However, similar rates of hematological adverse events were also observed in patients treated with AZA. Hepatotoxicity has been rarely reported. In the Tricontinental study (Keown, 1996) some cases of hepatitis occurred, although the cause was not specified. Hepatotoxicity was not reported in the European (Pichlmayr, 1995) nor in the US study (Sollinger, 1995).

Opportunistic infections can occur with MMF like with other immunosuppressive regimens, cytomegalovirus (CMV) being the most frequently reported pathogen (Hibberd, 1993). In the Tricontinental Study, the incidence of CMV syndrome was about 10 % during the first 6 months, which was comparable to the incidence in AZA treated patients (Keown, 1996), but slightly higher than in the placebo group (Pichlmayr, 1995). Severe CMV infections, however, have been reported more frequently in the MMF 3 g/day group than in the MMF 2g/day, AZA and placebo groups.

MMF has been used in previous clinical studies always in combination with other immunosuppressive drugs. The real incidence of adverse effects specific to MMF is therefore largely unknown and needs further evaluation.

2.1.3.2 Adverse event related MMF dose changes

Side effects or concurrent infections in organ transplantation often require dose reduction or even discontinuation of immunosupressive drugs, including MMF. Twelve percent of the patients enrolled in prospective kidney transplantation

trials discontinued MMF due to adverse effects related to the MMF therapy (Mele, 2000), but the influence of dose reductions on outcome was not separately analysed in these studies. More than half of patients in later studies have been required a MMF dose reduction due to side effects (Knoll, 2003; Squifflet, 2001). The most frequent reasons were leukopenia, diarrhea and infections. The reports on the long-term consequences of MMF dose reductions are controversial. Knoll et al.(2003) found no significant association between MMF dose reductions and allograft failures, although the cumulative number of days with reduced MMF dose was an independent predictor of acute rejection. Pelletier et al. found significantly higher rejection rate and decreased graft survival in 70 % of patients, who had at least one dose change, compared to patients with no dose changes (Pelletier, 2003). In particular, early MMF dose reductions are supposed to be associated with higher immunological risk.

2.2 Risk factors for kidney transplantation outcome

2.2.1 Recipient related risk factors

Acute rejection has been historically one of the main reasons of kidney allograft loss (Cole, 1995). Modern immunosuppressive therapies have greatly reduced the incidence of acute rejections and the detrimental effect of acute rejections on later graft survival (Matas, 2001; Tantravahi, 2007). Some authors have even reported no association between acute rejection episodes and outcome of transplantation (Isoniemi, 1994; Quiroga, 2006), especially if the rejection has been of mild severity (Oien, 2007). Nevertheless, still today, patients with late or severe rejections (Humar, 1999) or with multiple rejection episodes (Matas, 1994) are at increased risk for graft loss. *Retransplantation* seems to predict lower graft survival (Gentil Govantes, 2009), although there are reports on similar outcomes with primary and retransplantation (Gruber, 2009). There is no consensus on the impact of *HLA mismatches* as an independent risk factor (Yates, 2006), although some authors claim that the significance of HLA matching has diminished in the last decades (Su, 2004). Fully HLA-matched kidney transplants, however, have still shown better graft survival than completely HLA-mismatched grafts (Terasaki, 1988; Ojo, 1997; Cecka, 2001; Opelz, 2007). It is disputable whether single HLA matches improve outcome in recipients of marginal kidneys considering longer cold ischaemia times associated with matching (Alfrey, 2001).

With improved immunosuppressive therapy and substantially decreased rejection rate, non-immunological factors have increasingly been recognized to contribute to the development of chronic allograft dysfunction (Yates, 2006). Severe *overweight* has been reported to contribute to graft loss (Meier-Kriesche, 2002) and patient death through worse cardiovascular and metabolic profiles

(Sancho, 2007), through increase in rejection rate (Gore, 2006) or other complications (Lynch, 2009). There are, however, no generally accepted criteria for the upper body weight limit signifying increased risks in kidney transplantation. Different authors have proposed body mass criteria of BMI >25 (Meier-Kriesche, 1999), BMI >30 (Halme, 1997) or BMI >35 (Cacciola, 2008); 15 kg increase in recipient weight or 10 unit increase in recipient BMI has also been considered as a risk factor (Feldman, 1996). Long *dialysis period* prior to transplantation has been shown to deleteriously affect patient survival in several studies (Cosio, 1998; West, 1992), but its impact on death censored graft survival has not been established. The evidence to date demonstrates that better graft and patient survival can be achieved with preemptive transplantation (Meier-Kriesche, 2000; Witczak, 2009), but this is hardly attainable except with living donation. Studies examining the effect of pre-transplant *dialysis modality* on graft survival have produced conflicting results. It has been shown that peritoneal dialysis (PD) patients have less delayed graft function (Snyder, 2002; Cancarini, 2006) and lower risk for graft failure and lower risk for death compared with hemodialysis patients (Goldfarb-Rumyantzev, 2005). In several studies, however, graft survival was not affected by the dialysis modality (O'Donoghue, 1992; Cacciarelli, 1993; Cosio, 1998; Snyder, 2002). *Delayed graft function* (DGF), usually defined as the need for dialysis after transplantation, has been identified as one of the principal correlates of poor graft survival in deceased donor kidney transplantation (Ojo, 1997; Shoskes, 1998; Kyllonen, 2000), whereas many authors have found no such relationship (Marcen, 1998; Moreso, 1999). In a recent meta-analysis (Yarlagadda, 2009) the presence of DGF was associated with a 41% increased risk of graft loss. Several studies have not been able to demonstrate association between *recipient age* and the risk of later graft loss, although long-term patient survival is obviously worse with advanced recipient age (Foley, 2005). No increased risk of graft loss was found at the age over 50 (Kwon, 2004), 60 (Benedetti, 1994) or even 65 years (Sener, 2009). Prolonged *cold ischemia time* (CIT) has a negative impact primarily on early graft function, and not so much on long-term function or graft survival (Kyllonen, 2000; Lee, 2000). Nevertheless, in some studies long CIT has indicated reduced graft survival (Salahudeen, 2004; Quiroga, 2006), also in transplantations from younger donors (Hernandez, 2008). Epidemiological studies have found a relationship between *smoking* and risk of developing progressive kidney damage in non-transplant patient populations with diabetic and non-diabetic kidney disease (Muhlhauser, 1994; Pijls, 2001) as well as in patients without any previous kidney disease (Gambaro, 1998). Similarly, smoking may be an important preventable risk factor for reduced kidney graft survival (Matas, 2001; Sung, 2001).

Thus there are many discrepancies regarding the relevance of aforementioned risk factors. Different transplant centers differ from each other in their kidney donor and recipient populations, allocation policies etc., the center effect may account for nearly 30% of all assignable variation in 1-year outcome

(Gjertson, 1990). Therefore the purpose of this study was to clarify the most important risk factors specifically for Estonian transplant population.

2.2.2 Donor risk factors

2.2.2.1 Trends in deceased organ donation

The number of patients with end-stage kidney disease waiting for a kidney transplant continues to increase world-wide. Different registry data show persistent shortage of donor organs available for transplantation. In the US the total number of donors increased 7% annually from 1996 to 2001, but the waiting list at the same time grew by 11% per year (Nathan, 2003). In the UK the waiting list expanded over 40 % during the last decade (Galliford, 2009). The growth is apparent only in transplantations from living donors, while the number of standard-criteria brain-dead donors has remained stable (Knoll, 2008). The criteria for deceased donor acceptance have changed dramatically during the two last decades. The most substantial change has taken place in acceptance of increasingly older donors (Chakkera, 2009). Three decades ago a donor age over 30 years was a major reason for declining a deceased kidney donor offer (Lucas, 1987). Over half of donors aged 51–60 years were not accepted, while donors older than 60 years were rare exceptions. Only 5 years later the discard rate had decreased to 25% in the former age group (Cecka, 1993). The deceased donor profile continues to shift from the young adult with traumatic head injury to the older adult with a cerebrovascular accident (Sung, 2008). Mean donor age and the proportion of older donors have increased in the US (Sung, 2008), in Canada (Badovinac, 2006) as well as in the Eurotransplant area (Smits, 2002).

The continuously increasing need for organs led to the reintroduction of the principle of donation after cardiac or circulatory death (DCD) in the early 1990s (Arnold, 1993). Over 40% rise in the number of donations after cardiac death has compensated for the decline in the number of kidneys from heartbeating donors (Nathan, 2003).

2.2.2.2 Donor factors and early graft function

DGF is a frequent complication in the post-transplant period, which is associated with morbidity, prolonged hospitalization and higher transplantation costs (Almond, 1991). The causes of DGF are mainly related to organ donor and procurement, but recipient risk factors, like hypovolaemia, can add to development of DGF (Perico, 2004).

Donor factors that may affect DGF are mostly the same that influence long-term results: high donor age and prolonged cold ischaemia time (Ojo, 1997; Humar, 2002; Lebranchu, 2005), kidney donation after cardiac death (Irish,

2003), history of diabetes, hypertension (Di Paolo, 2002) or cardiovascular disease (Verran, 2001). Additional factors that impair recovery of kidney function are inotropic support of the donor (Marshall, 1996), cold storage preservation type (Shoskes, 1996) and female donor to male recipient combination (Boom, 2000). The impact of many donor variables has been summarised in nomograms that quantify the likelihood of DGF (Irish, 2003).

Without changes in formal policy, donors with previously absolute contraindications are increasingly used, but the possible consequencesof this for our transplant patients need further evaluation.

2.2.2.3 Donor risk factors and long-term graft outcome

Retrospective registry-based studies have identified many prognostic factors of living and deceased donors that affect graft survival in kidney transplantation. *Donor age* is one the most significant predictors of kidney transplant outcome, although an age limit with significantly worse outcomes varies in the reports: ≥55 (Alexander, 1994; Carter, 2000), >60 (Terasaki, 1997; Sola, 1998) or >70 (Chavalitdhamrong, 2008). Kidneys from older donors can have near-normal histology and after transplantation a comparable survival with kidneys from younger donors (Nghiem, 1993; Escofet, 2003). Even kidney transplants from deceased donors older than 75 years have shown acceptable performance and can be considered for use in older recipients (Foss, 2009). Several studies have shown that a pretransplant histological evaluation of kidneys from donors older than 60 years help to achieve excellent long-term outcomes (Andres, 2000; Remuzzi, 2006). It has been suggested that close *age matching* between donor and recipient may improve graft survival (Waiser, 2000), although other authors have not found a significant advantage of this factor (Newstead, 1992). Swanson et al. suggested to donor/recipient age ratio over 1.1 to be used as a marker of increased hazard ratio for graft loss (Swanson, 2002). Kidney transplants from *female donors* have somewhat lower graft function and survival compared with grafts from male donors (Zeier, 2002; Kim, 2004), particularly in male recipients. *The source of kidneys* influences transplant outcomes**.** Use of kidneys from living donors ensures better graft survival (about 5–10% at one year) compared with use of kidneys from deceased donors (Hariharan, 2000; Kim, 2004) in large recipient age groups, including geriatric recipient cohort (over 75 years)(Macrae, 2005). Donation after cardiac death gives graft survival comparable to graft survival in transplantations from brain dead donors, although with a significantly higher DGF rate (Nicholson, 2000; Barlow, 2009). Donor history of *hypertension* is obviously a risk factor for graft failure (Pessione, 2003), but the impact of its duration is unclear. Particularly important is longstanding hypertension and hypertension with preexisting suboptimal histology (Di Paolo, 2002), whereas a recent history of elevated blood pressure is apparently not detrimental (Carter, 2000; Ojo, 2000). Cerebrovascular accident as the *cause of death* has proved to be a risk factor for lower GFR (Nyberg,

2001) as well as for graft failure (Cecka, 1988; Port, 2002; Rao, 2009) although according to some studies the long term impact is insignificant (Kyllonen, 2000).

The concept of *expanded criteria donors* (ECD) has been used to define high-risk donors (Port, 2002). ECD covers four donor characteristics that are independently associated with an increased risk of graft failure compared to standard donors: all donors aged 60 years and older; those aged 50 to 59 years with at least two of the other three conditions (cerebrovascular cause of death, serum creatinine >1.5 mg/dL or hypertension). The transplantation outcomes with ECD kidneys, however, are not necessarily worse than those with standard criteria kidneys. Stratta et al. found similar patient and graft survival rates and graft function up to 18 months for transplantations from ECDs and from all other donors (Stratta, 2004). Despite increased risks, transplantations from ECD can still offer substantial survival advantage (in average 5 years) over maintenance on dialysis for the end-stage kidney disease patients (Ojo, 2001).

Although recipient comorbidities as prognostic markers have been studied by many authors (Jassal, 2005; Hernandez, 2005; Kauffman, 2007), the effects of *donor comorbid conditions* have not thoroughly been investigated. Loven et al. investigated whether information about donor comorbidities predicts graft survival (Loven, 2003). Combination of risk factors was associated with decreased graft function at one year, but did not affect graft survival.

2.2.2.4 Donor risk factors and baseline kidney histology

Aging is associated with morphologic changes in the kidney, contributing to glomerular enlargement and glomerulosclerosis (Anderson, 1986; Kasiske, 1987; Li, 2002), but also to arterial intimal sclerosis and hyaline arteriolosclerosis (Tracy, 2007), tubular atrophy and increase in the interstitial volume with interstitial fibrosis (Silva, 2005). Tan et al. studied recently kidney senescence in donor kidneys and found more glomerulosclerosis and glomerular enlargement in old donors (over 55 years), who also exhibited decreased graft GFR by 1/3 compared to donors under 55 years (Tan, 2009).

Hypertensive nephrosclerosis is the second most common cause of end-stage kidney disease (Hill, 2008). Elevated blood pressure is associated with vascular (Zhou, 2008) and glomerular lesions (Hill, 2008). Arteriolar changes lead to ischemic glomerulosclerosis, which increases linearly with increasing blood pressure (Griffin, 2004). Malignant hypertension is characterized morphologically by proliferative endarteritis and vascular fibrinoid necrosis (Schwartz, 1987).

Type 1 *diabetes* leads to diabetic nephropathy in about 45 % of cases (Grenfell, 1986) and is therefore usually considered as contra-indication to kidney donation. The most important structural changes in type 1 diabetes involve the glomeruli while type 2 diabetic patients typically have normal glomerular structure with or without tubulo-interstitial and/or arteriolar abnormalities

(Fioretto, 2007). Typical glomerular lesions are thickening of glomerular basement membrane and mesangial expansion, which may be associated with nodular lesions compressing the associated glomerular capillaries (Kimmelstiel-Wilson nodules) (Dalla, 2000). *Predonation estimated GFR* is a readily available parameter for donor kidney assessment, but seems to be unrelated to kidney histology (Karpinski, 1999), mostly because several transient conditions can increase plasma creatinine concentration significantly (Randhawa, 2001). Severe *obesity* of the donor may be an additive risk factor (Serra, 2008) in cases with preexisting nephropathy (Bonnet, 2001) or reduced kidney mass (Praga, 2000). Despite increased glomerular size, it has been reported that obese individuals have shown the same proportion of completely sclerosed glomeruli as their non-obese counterparts (Kasiske, 1985; Rea, 2006). Cigarette *smoking,* as a risk factor for atherosclerosis (Djousse, 2002), influences the kidney primarily through myointimal hyperplasia of small arteries (Lhotta, 2002), but no effect on glomerulosclerosis has been described.

The impact of concomitant comorbidities and other risk factors on kidney structure have been studied in different disease groups but not in the context of organ donor population, nor has the influence of donor factors on CADI score been investigated.

2.3 Baseline kidney histology and transplantation outcome

Several studies have investigated the utility of donor implantation biopsy to predict long-term kidney allograft outcome, but the results have varied from one study to another; the weaknesses of many studies are small patient number or short follow-up time. One of the reasons for conflicting results is intra- and interobserver variability and poor reproducibility of semiquantitative grading of kidney biopsies (Marcussen, 1995; Furness, 2003). Although morphometry has been proposed to overcome this problem, further studies have not confirmed any better predictive value of the morphometric evaluation of donor biopsies compared to the semiquantitative grading (Lopes, 2005). Interpretation of kidney transplant biopsies is standardized by Banff classification of kidney allograft pathology, which is the most widely used classification of transplant pathology and today required for study reports to be published in international journals. The Banff classification defines the key lesions and their scoring in different compartments of the kidney (Racusen, 1999). It was introduced first of all for assessment of acute changes and rejection and was not designed for donor biopsy interpretation. Although the last update suggested to use the Banff scheme also in baseline biopsies, it did not define prognostic significance of the Banff schema in pre-transplantation setting (Solez, 2008).

2.3.1 Early graft function

Discrepancies persist regarding the short-term prognostic value of suboptimal donor histology, which reflects the significance of other donor, recipient and transplantion related factors. Studies from the early 1990-ies found no association between baseline biopsy findings and early graft function (Curschellas, 1991; Lehtonen, 1999). Gaber et al. were the first who stated that glomerulosclerosis (GS) > 20% increases significantly the risk of DGF (Gaber, 1995) but several further studies did not confirm this (Matignon, 2008). Some studies report no impact of arteriolosclerosis on the rate of DGF (Curschellas, 1991; Pokorna, 2000), but there are also data supporting the correlation of DGF with fibrous intimal thickening (Karpinski, 1999; Lopes, 2005) and arteriolar hyalinosis (Wang, 1998; Matignon, 2008). There are few studies suggesting potential association between early graft function and tubulointerstitial changes (Di Paolo, 2002).

2.3.2 Long-term outcome

The negative impact of donor vascular lesions on posttransplant graft function (Minakawa, 1996; Bosmans, 2000) and survival (Taub, 1994) have been stressed by some authors but questioned by others (Randhawa, 2000). Both arteriolar hyalinosis (Wang, 1998; Munivenkatappa, 2008) and arteriosclerosis (Kayler, 2008), in particular, severe arteriolosclerosis (Pokorna, 2000), have been identified as vascular changes with a prognostic value.

Some studies have emphasized the importance of GS in predicting graft function (Randhawa, 2000) and survival (Escofet, 2003; Cicciarelli, 2005), while others have not seen a connection (Sund, 1999; Pokorna, 2000). A numeric cut-off value for an unacceptable GS remains disputable. Some authors have suggested 20% GS as the limit for kidney donation (Gaber, 1995), while other authors have found a similar graft survival in this patient group compared to patients with kidneys with lower rate of GS (Wijnen, 1995; Lu, 2000).

Also the predictive value of chronic tubulointerstitial alterations in baseline biopsy specimens is controversial. Whereas some authors have regarded interstitial fibrosis as a marker for poor graft function (Seron, 1993; Randhawa, 2000; Chapman, 2005) and survival (Arias, 2007), others have not found such association (Wang, 1998).

Several scoring systems for donor kidney biopsy findings have been generated. A combined donor chronic damage score, consisting of GS, vascular intimal sclerosis and interstitial fibrosis scores, has been proposed to predict short-term risk for graft loss (Lopes, 2005; Ibernon, 2007). Further, Remuzzi proposed to quantify the severity of donor kidney damage with a score, which includes glomerular sclerosis, tubular atrophy, interstitial fibrosis, arteriolar narrowing, ranging from 0 to a total of 12 (Remuzzi, 1999). Remuzzi's scoring system was later supported by Snoeijs et al. in a report on kidney trans-

plantations from donors after cardiac death (Snoeijs, 2008). Re et al. however, comparing clinical and histopathological scores in donor kidney evaluation, found no association between pretransplant Remuzzi score and graft survival (Re, 2006).

In the Maryland Aggregate Pathology Index some other parameters, not defined in Banff classification, have been used; for example presence of peri-glomerular fibrosis or scar, which were also found to be associated with increased risk of graft loss (Munivenkatappa, 2008).

Studies on post-transplant follow up biopsies indicate that CADI may be a good correlate of further graft function (Ortiz, 2005) and survival (Yilmaz, 2003). The first report on the CADI score in implantation kidney biopsies found that CADI may predict long-term graft function, although it does not affect delayed graft function rate (Lehtonen, 1999). Anglicheau et al., in a recent study compared clinical (Nyberg and Pessione) and histological (CADI, Banff and Pirani) donor assessment scores and found the CADI score, unlike clinical scores, to be correlated with posttransplant GFR (Anglicheau, 2008).

The contradictory results about histologic parameters, as well as the predictive value of the CADI score, require clarification in a large study population, which was attempted in our study.

3. AIMS OF THE STUDY

The principal aim of the study was to examine the factors affecting kidney graft survival and the options of improving long-term results after kidney transplantation.

The specific aims were:

1. To examine the current trends in deceased kidney donation and the impact of donor factors on transplantation outcome.
2. To explain the influence of donor risk factors and comorbidities on baseline kidney morphology and on the CADI score.
3. To investigate the predictive value of histological parameters and the CADI score in donor baseline biopsies for post-transplant outcome.
4. To assess the efficacy of early conversion from AZA to MMF treatment as rescue therapy in patients with high immunologic risk. To clarify the impact of transplantation related factors on graft survival in kidney transplant population.
5. To investigate the safety of MMF treatment and the impact of adverse event-related dose reductions on rejection rate and graft function.

4. MATERIALS AND METHODS

The thesis is based on 4 different studies performed in Tartu University Hospital and in Helsinki University Hospital. The Ethics Committee of Tartu University approved study I and the Ethics Committee of Helsinki University Hospital approved the study protocol for studies II–IV.

4.1 Patients

Tabel 1. Summary of patient populations in four studies

Publication	No.of patients included	Site	Period of data collection	Follow-up time
I	137	Tartu	1996–2001	6 years
II	407	Helsinki	1992–2003	6 months
III	1119 deceased donors 2006 kidney recipients	Helsinki	1991–2003	1 year
IV	481 deceased donors 829 kidney recipients	Helsinki	1995–2005	3 years

The presented publications were retrospective clinical studies of kidney transplantations. Patients from Helsinki University Hospital partially overlap in studies II–IV.

The population of **study I** comprised 178 deceased donor kidney transplant patients in Tartu University Hospital between January 1996 and June 2001. Six transplants were never functioning and 35 patients were switched to MMF later than 3 months after transplantation and those 41 transplantations were therefore excluded, which makes the final number of study subjects 137.

All patients received cyclosporine (CyA) and methylprednisolone (MP) according to the standard protocol in Tartu University Hospital. The patients were analysed in two groups (Table 1 in publication I): those who received AZA (AZA group, n=72) and those who were started with MMF as primary therapy (highly immunized patients, n=17) or were switched from AZA to MMF (n=48) within 3 months (MMF group, n=65). Patients were switched to MMF in case of early severe rejection (according to the Banff classification – Ib or more, n=35) or AZA intolerance (n=13).

Study II covered 415 kidney transplantations in adult recipients in Helsinki University Hospital between September 1992 and September 2003, whose initial triple immunosuppression contained MMF. Eight patients were excluded from the analysis because of transplantectomy and cessation of immunosuppression within the first post transplant week. Detailed information of 407 kidney transplantations is given in Table 1 in publication II.

The population of **study III** consisted of 1209 deceased heart-beating donors in Finland between January 1991 and December 2003. Ninety donors were excluded from the study, as both their kidneys were sent to other transplant centers of Scandiatransplant on the basis of exchange obligation rules or discarded as unsuitable for transplantation. Thus the final analysis included 1119 donors and 2006 transplantations of their kidneys (Table 1 in publication III).

In **study IV** 1134 deceased kidney donations in Finland from August 1995 to December 2005 in were examined. In this period baseline biopsy was taken from 543 donors. Of the biopsies, 481 with at least 7 glomeruli and at least one artery, were included in the final analyses. The 829 kidney transplantations using these kidneys were examined. Baseline characteristics of the study population are in Table 1 in publication IV.

Standard immunosuppression consisted of calcineurin inhibitor, MMF or AZA and methylprednisolone started before the transplant surgery. In Tartu University Hospital all patients received CyA, in Helsinki University Hospital both CyA and Tacrolimus (TAC) were used (CyA 64.9% in study II; 85% in study IV). The initial dose of CyA was 10 mg/kg/d, and the dose was adjusted to achieve a target level 200–300 ng/ml. TAC was initiated at 0.2 mg/kg/day, with the dose adjusted to achieve a target level of 10 to 15 ng/ml. MMF standard dose was 1 g b.i.d. for CyA patients and 0.5 g b.i.d. for TAC patients. All patients received intravenous methylprednisolone 250 mg preoperatively followed by oral methylprednisolone.

The diagnosis of all acute rejections was based on biopsy findings. The initial treatment for acute rejection was intravenous methylprednisolone 500–125 mg/d for 3–5 days. In steroid resistance or vascular rejection, anti-lymphocyte antibodies were used (OKT-3 or ATG).

4.2 Data collection

Clinical data about donor medical history and treatment, recipient characteristics and transplantations were colleted from original hospital documents, from the medical record database in Tartu University Hospital and from The Finnish Kidney Transplantation Registry database. Kidney function was measured by serum creatinine concentration and estimated GFR: Cockcroft-Gault formula (Cockcroft, 1976)was used for adults and Shull formula (Shull, 1978) for children. A kidney graft was considered as failed when the patient returned to maintenance dialysis, when the graft was removed, or when the patient died with a functioning graft.

In **study I** the following data were collected: donor age, recipient age, recipient gender, HLA mismatch, DGF, length of time on dialysis, dialysis mode, previous transplants, CIT and rejection episodes during the first 3 months. There were no full HLA-matched kidneys in the study population and 9% were six HLA-Ag mismatched. Follow-up data on the medication (CyA

dose and serum trough level, use of statins and antihypertensive medication), graft function (serum creatinine) and other patient variables (serum cholesterol level, blood pressure) were recorded at one year and graft survival was recorded up to 6 years after transplantation.

In **study II** gastrointestinal, haematological and infectious adverse events, hepatotoxicity (elevated serum ALAT), MMF dose changes and their causes during the first 100 post-transplant days were registered. Limits for abnormal laboratory values for this study were set as follows: platelet count $<100 \times 10^9$, leukocyte count $<3.0 \times 10^9$, ALAT >60 U/l. MMF dose was reduced on clinical grounds for presumed side effects, the dose restoration was attempted when the side effects resolved. In case of severe or persistent side effects MMF was discontinued temporarily or permanently. Kidney transplantion outcome was measured with acute rejection rate, graft function and survival during first 6 months.

In **study III** data were collected about donor medical history, donor treatment during hospitalization, donor management after brain death and during the organ recovery process. Kidney transplantation outcome was measured using the onset of graft function (DGF classified by Humar et al.(Humar, 2002)), patient and graft survival up to 1 year. The mean donor age was 41 years (men 39.4 years, women 43.5 years). Overall, 60.4% of the donors were men. Mean time on the ventilator was 40 hours (median 23.4 hours), mean interval from death to organ retrieval was 9.5 hours, and multiorgan retrieval was done in 54%. The main causes of death were intracranial bleeding (55%), low-energy (19%) and high-energy (11%) brain injury, gunshot (4%), and cerebrovascular thrombosis (4%). Three percent of donors were known to have had coronary artery disease and 17% had had hypertension.

Detailed information and definitions of the donor risk factors in **study IV** can be seen in publication IV.

In order to see whether there was a significant selection bias, we compared the donor population of this study with the kidney donors (n=602) without baseline biopsy for the same time period. There were no significant differences in donor age, gender or cause of death between the donor groups. The UNOS criteria were used for expanded-criteria donors (ECD): age 60 years and older, or age 50–59 years with at least two of the following conditions: cerebrovascular accident as the cause of death, plasma creatinine higher than 1.5 mg/dl or a history of hypertension (Port, 2002).

4.3 Histological investigation of baseline biopsies

During 1995–1999 a baseline biopsy was not a standard procedure in the Helsinki University transplant center and was taken at the discretion of the transplant surgeon at the end of the recipient operation (n=120). From 2000 on, biopsies (n=361) were routinely taken during the donor operation before the *in situ* perfusion. Bard Magnum automatic gun with an 18 gauge needle was used.

Specimens were embedded in paraffin, sectioned and stained in a routine way with hematoxylin and eosin, periodic acid-Schiff, Masson's trichrome and Silver Jones. The components of CADI, as well as arteriolar hyalinosis (ah), were graded semiquantitatively from 0 to 3 according to the Banff 97 classification (Racusen, 1999). CADI may take a value between 0–18 and is a sum of the scores for interstitial inflammation (i), tubular atrophy (ct), vascular intimal proliferation (cv), interstitial fibrosis (ci), mesangial matrix increase (mm) and percentage of sclerotic glomeruli (Isoniemi, 1992). For CADI the percentage of sclerotic glomeruli was scored from 0 to 3 as follows: no sclerotic glomeruli – 0, < 15% sclerotic glomeruli – 1, 16–50% sclerotic glomeruli – 2, >50% sclerotic glomeruli – 3. Allograft glomerulopathy and mesangial matrix increase as signs of glomerular pathology were very rare in our material and were therefore excluded from this analysis. All biopsies were scored by one pathologist.

4.4 Statistical analysis

Differences in the mean values were tested with Student´s *t*-test; nonparametric Mann Whitney test was used for unequal variances. Fisher's exact test was employed for binary categorical variables. Chi-squared test were used to compare proportions between groups. Simple linear regression analysis was used to investigate correlations between two continuous variables. Graft survival time was analysed with the Kaplan-Meier method, group comparisons were performed with the log-rank test. Graft survival in study IV was censored for patient death with functioning graft. Multivariate survival analysis was performed with multiple linear regression and with the Cox proportional hazard regression. A stepwise selection method was used to identify a model including the variables, which were significantly associated with graft loss. A two-sided p-value of < 0.05 was considered statistically significant. Statistical analyses were performed with the SAS version 8.1 in study I, Statistica 6.0 in studies II and III and Statistica 7.0 in study IV.

5. RESULTS

5.1 Deceased donor trends and impact of donor risk factors on transplantation outcome

Deceased donor trends

Mean donor age increased from 33 to 47 years during the study period (Table 2 in publication III). The proportion of female donors increased from 33% to 47%. Mean hospitalization time remained constant at about 50 hours, but there was a significant increase in the time on ventilator from just over 30 to nearly 50 hours. Throughout the study period the proportion of donors with many risk factors increased, e.g. coronary artery disease, hypertension, smoking, alcohol abuse, cardiopulmonary resuscitation and surgical or radiological interventions before death. In contrast, hypotensive episodes and oliguric periods decreased. Mean serum creatinine concentration of the donor was 74 μmol/l (range 22 to 195). Cytomegalovirus (CMV) seropositivity was found in 77% of the donors.

Donor risk factors and transplantation outcome

The onset of graft function was immediate in 53%, slow in 14%, and delayed in 31% of cases. In 2% of the cases the graft never functioned. Graft function was significantly better in transplantations from young donors with trauma as the cause of death, donors without hypertension and coronary artery disease and with short stay on ventilator. More detailed data are given in Table 3 in publication III.

The 5-year graft survival was 84% for transplantations from CMV-negative donors versus 79% from a CMV-positive donor. CIT, donor age and hypertension had an independent effect on graft function in multivariate analysis, but not on graft survival. Also donor CMV status had an independent effect on graft function. On multivariate Cox regression, donor CMV status and donor age were significant factors affecting long-term graft survival. When, however, patient deaths with a functioning graft were censored, only donor CMV status remained significant. Despite the changes in donor quality the 1-year results improved significantly during the study period; graft survival improved from 91% to 96% and creatinine from 121 μmol/l to 109 μmol/l.

Cumulative co-morbidities and transplantation outcome

The number of positive donor risk factors was correlated with the rate of DGF ($p < 0.0001$) and with GFR at 3 years ($p = 0.003$) (Figure 1). Transplantations from donors with >4 risk factors (n=67) showed significantly decreased graft survival compared to those with 0–4 risk factors; the values of five-year death censored graft survivals were 83% and 93%, respectively (p=0.041).

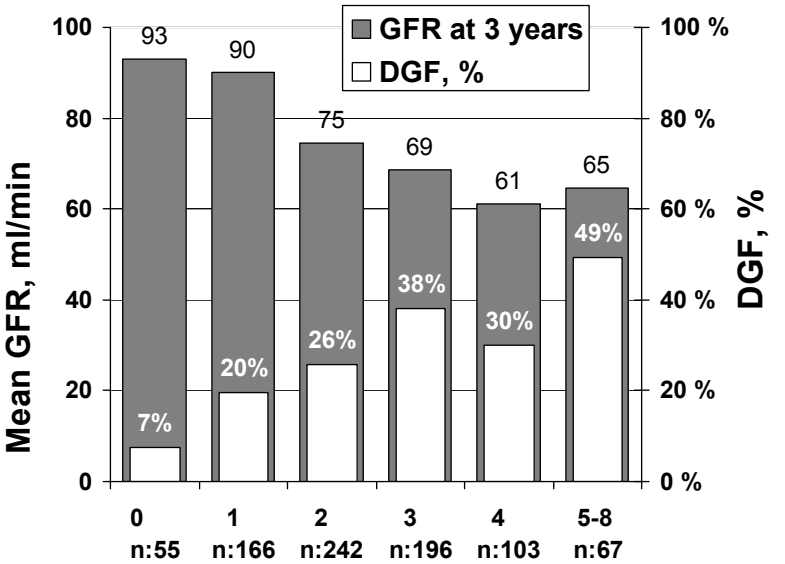

Figure 1. Transplant outcome by number of donor risk factors. GFR, glomerular filtration rate; DGF, delayed graft function

5.2 Influence of donor risk factors on baseline kidney morphology

Biopsy results

Distribution of Banff scores of different histological findings in 481 donor biopsies is shown in Table 3 in publication IV. No pathology in any studied histological parameter was found in 177 (37%) donor biopsies. The average number of glomeruli in the biopsies was 16.4±6.7 (range 7–40). No GS was seen in 319 (66%) biopsies. Severe GS (>20%) was found in 7.5% of the extended-criteria and in 1.9% of the standard-criteria donors.

Predonation risk factors and donor kidney histology

Donor age was the most significant among the studied clinical risk factors affecting all distinct histological parameters and the CADI score (Table 2). Mean CADI score was 0.65 in donors aged < 50 years and 1.12 in donors aged ≥ 50 years ($p<0.001$). Donor age remained an independent risk factor for all variables also in multivariate analysis. Cerebrovascular cause of death predicted vascular damage (odds ratio 2.03) and higher CADI (odds ratio 1.91). Hypertension and pre-donation GFR which were important for CADI in univariate analysis, turned out to be insignificant in multivariate analysis.

Table 2. Results of univariate logistic regression analysis expressed as odds ratios (OR) and results of linear regression expressed as standard coefficients (SC) for each independent variable with the histological parameter as the dependent variable.

Donor data	**%GS**	**ct**	**ci**	**cv**	**ah**	**CADI 0–1 vs. >1**
	SC			**OR**		
Age	**0.14**[1]	**1.06**[1]	**1.02**[1]	**1.03**[1]	**1.03**[1]	**1.06**[1]
Cause of death: Cerebrovascular vs. other	**1.34**[1]	1.55	1.39	**2.67**[1]	**2.53**[1]	**2.16**[1]
Atherosclerosis	1.91	0.84	0.00	0.75	2.26[2]	0.88
Ischemic heart disease	**2.52**[1]	1.88	0.82	0.72	1.55	1.44
Treated hypertension	**1.91**[1]	1,43	1,00	1,12	1,43	1,46
Untreated hypertension	**2.48**[1]	0.57	1.30	**2.06**[1]	1.55	**2.88**[1]
Resuscitation	–0.33	0.31	0.62	1.26	1.32	0.64
Hypotonia	0.27	**2.61**[1]	**2.24**[1]	0.76	0.78	1.29
Oliguria	–0.99	0.00	1.87	0.66	1.09	1.35
Smoking	0.71	2.25	1.88	**2.01**[1]	**2.41**[1]	1.66
Alcohol abuse	–0.03	0.72	0.35[2]	0.78	0.65	0.60
Donor GFR	**–0.022**[1]	0.9933	0.9944	**0.9931**[1]	**0.9926**[1]	**0.9898**[1]

[1] $p<0.05$; [2] $p<0.1$. ct, tubular atrophy; ci, intestitial fibrosis; cv,vascular intimal sclerosis; ah, arteriolar hyalinosis; %GS, glomerulosclerosis; GFR, glomerular filtration rate

In young (<50 years) donors with traumatic brain death, we found no biopsies with severe GS, compared to 6% in the old donors with cerebrovascular accident as the cause of death ($p< 0.0001$). Moreover, in the younger donor group only 28 % of the subjects had a CADI score of 1 or more, compared to 69 % in older donor group.

ECDs had significantly higher scores for vascular and glomerular compartments and CADI than standard criteria donors. Transplantation from these donors resulted in worse graft survival: the 5-year death censored graft survival was 89 % in transplantations from ECD compared to 93 % in transplantations from standard criteria donors ($p = 0.028$).

Impact of donor risk factors and co-morbidities on donor kidney histology

When the number of donor risk factors increased from zero to six, the mean CADI increased from 0.5 to 1.4 ($p = 0.0003$) and GS increased from 1.5% to 8.1% ($P < 0.0001$, Figure 2). The impact on vasculopathy (cv, ah) and tubular atrophy (ct) scores was found to be similar.

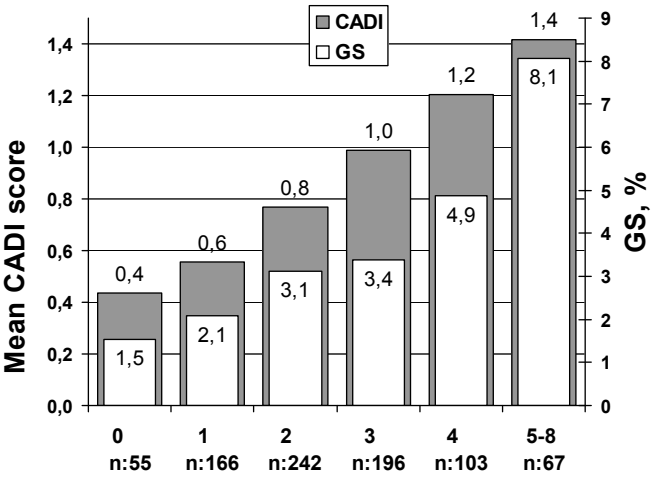

Figure 2. Baseline kidney histology by number of donor risk factors. GS, glomerulosclerosis

5.3 Predictive value of histological parameters or CADI score of donor kidney on post-transplant outcome

Glomerulosclerosis (GS)

The 5 year death censored graft survival was 93% in transplantations with <20% GS in donor kidney whereas it was 82% if the GS was ≥20% (hazard ratio 2.5, log-rank test p = 0.028). Including in the analysis only transplantations with kidneys with at least 10 glomeruli, the predictive value of GS on graft survival increased (hazard ratio 3.2, p= 0.012).

GFR at 1 and 3 years was inversely correlated with the percentage of GS (Table 3). Neither GS nor the other individual histological parametres shown in Table 3 were not predictive for DGF.

Table 3. Difference of mean GFR (Δ GFR) in patients with histological score 1 or more in single compartments compared to patients with score 0

	1 year GFR		3 year GFR	
Histological variable	**Δ GFR**	**p-value**	**Δ GFR**	**p-value**
ct	–12.5	0.013	–10.8	0.013
cv	–6.3	0.003	–4.3	0.022
ah	–9.0	<0.001	–7.0	0.002
ci	–5.8	0.052	–4.5	0.08
% GS				
1– 9 %	–6.8	0.007	–5.2	0.049
10– 19%	–9.1	0.004	–9.7	0.001
≥ 20%	–19.1	<0.001	–19.7	< 0.001

CADI

In the transplantations with kidneys with CADI score 0–3, the rate of DGF was 28% whereas it was 52% if the CADI score was over 3 (p=0.015). The correlation between CADI and graft function up to 3 years is depicted in Figure 3. CADI score over 3 was also predictive for long-term graft survival: 5-year graft survival was 92% in CADI 0–3 and 84% if the CADI score was 4–6 (p = 0.056).

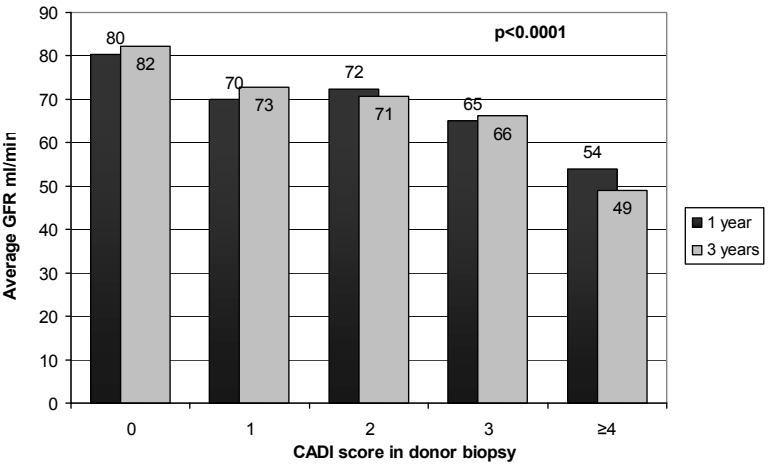

Figure 3. Estimated glomerular filtration rate (GFR) at one and three years in different baseline CADI categories

Arteriosclerosis

Arteriolar hyalinosis, but not vascular intimal proliferation had an impact on graft survival. Both cv and ah were associated with worse graft function (Table 3). The predictive value of high vascular score (>1) on graft function was analysed separately. With ah scores 0, 1 and 2 to 3, the mean GFR at 3 years was 73 ml/min, 67 ml/min (NS) and 62 ml/min (P = 0.003), respectively. With cv scores 0, 1 and 2–3 mean GFR at 3 years was 74 ml/min, 69 ml/min (P = 0.07) and 56 ml/min, respectively (P = 0.0005).

Tubulointerstitial changes

Tubular atrophy and interstitial fibrosis correlated with graft function up to 3 years but had no predictive value for graft survival.

In a multivariate analysis of the impact of histological parameters on GFR, we found that GS, cv and ah were significant independent factors predicting GFR at 1 year but only GS and ah remained significant at 3 years (Table 6 in publication IV).

5.4 Efficacy of early conversion to MMF in high risk patients and recipient related risk factors for graft survival in kidney transplant population

A statistically significant difference between the MMF and AZA groups was revealed in the following characteristics: the mean recipient age in MMF group was 8.5 years lower and there were more retransplantations in the MMF group (Table 1 in publication I). As the main indication for MMF treatment in the study cohort was high immunological risk (retransplant) or early acute rejection, it was reflected also by the higher 3-month acute rejection rate in the MMF group (68%) compared to the AZA group (32%). 80% of the rejection episodes in the MMF group, however, occurred during AZA treatment before switching. Patients starting with MMF immediately after transplantation had 41% rejection rate (7/17).

According to the Kaplan-Meier analysis, graft survival for the AZA and MMF groups was 79% and 85% at 1 year, and 51% and 67%, respectively, at 6 years (p=0.046) (Figure 4).

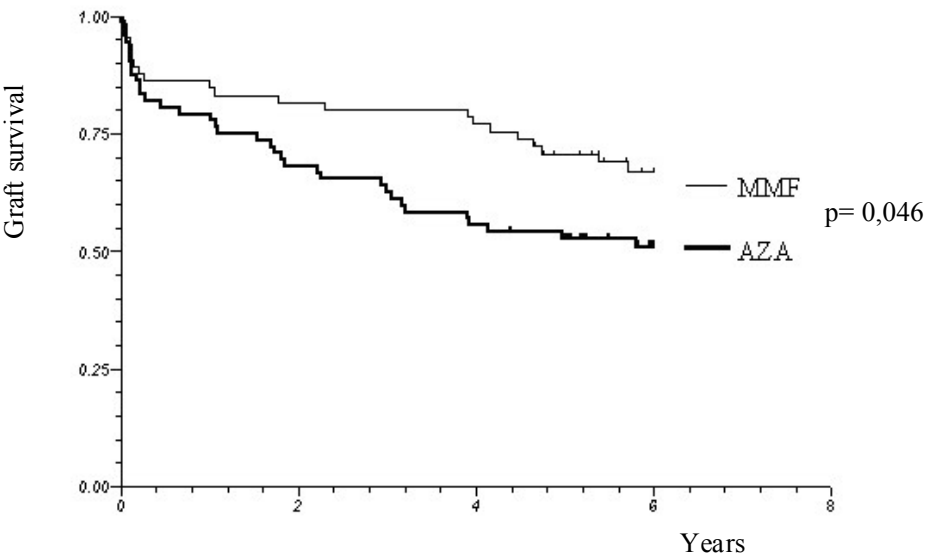

Figure 4. Kaplan-Meier estimates of graft survival in MMF and AZA groups

Comparison of the follow-up characteristics in both groups at year 1 shows that in the MMF group the mean cholesterol level was 1.0 mmol/l lower (p=0.002) and mean systolic blood pressure was 11 mmHg lower compared to the AZA group (p=0.009) (Table 2 in publication I). Although the proportions of the patients who received statins and hypotensive medicines were somewhat

smaller in the MMF group, this difference was not significant. Despite the significantly lower CsA daily dose (p=0.015) in the MMF group, mean serum creatinine was similar in both groups.

In univariate Cox proportional hazard analysis donor age, dialysis mode and therapy type (AZA or MMF) proved significant factors for graft survival. The inclusion of the variables with p<0.25 in the multivariate model revealed that only onset of graft function and therapy type proved to be significant factors for 6-year graft survival (Table 4). The multivariate Cox survival model demonstrated that irrespective of recipient age, MMF therapy reduced the relative risk of transplant loss by 34% (p=0.028), while DGF increased the risk to 2.26 (p=0.009). The other risk factors (recipient age, dialysis time, donor age, HLA mismatch etc.) proved non-significant.

Table 4. Results of uni-and multivariate analysis of the risk factors for graft survival

	Risk factor	Crude hazard ratio	95% CI	*p* value
Univariate analysis	Female donor	1.23	0.61 – 2.10	0.7
	Donor age (per 10 years)	1.21	0.99 – 1.48	0.072
	Female recipient	0.90	0.51 – 1.59	0.7
	Recipient age (per 10 years)	1.09	0.88 – 1.34	0.4
	HLA mismatch: >3	0.93	0.55 – 1.59	0.8
	Dialysis mode: hemodialysis	1.35	0.79 – 2.30	0.065
	Dialysis time (per year)	0.92	0.73 – 1.15	0.5
	Ischemia time (per hour)	0.99	0.94 – 1.04	0.6
	Delayed graft function	2.10	1.14 – 3.85	0.016
	Early acute rejection	1.08	0.64 – 1.84	0.8
	MMF treatment	0.57	0.34 – 0.99	0.046
Multi-variate analysis	Delayed graft function	2.26	1.22 – 4.16	0.009
	MMF treatment	0.54	0.31 – 0.94	0.028

5.5 MMF intolerance and its impact on transplantation outcome

5.5.1 MMF adverse events

Adverse events (AE) occurred in 322/407 transplantations (Figure 2 in publication II). The most common AE was elevated ALAT-value occurring in 202 transplantations (50%). Considerable ALAT-increase, over 120 U/l, occurred in 86 transplantations (21%). Gastrointestinal complaints occurred altogether in 139 transplantations (34%). In 85 transplantations (21%) the recipient had at least one episode of diarrhoea. Other AEs are described in detail in the original publication II.

The AEs mainly occurred in early stages after transplantation. Of all AEs, 77% occurred within 3 weeks of transplantation. The timing of AEs was different: over 80% of hepatotoxicities, diarrhoeas and other abdominal complaints occurred within three weeks of transplantation, whereas only 1/3 of infections occurred as early as that.

We compared the incidence of AEs separately in CyA and TAC patients (Table 2 in publication II). Elevated ALAT-values and thrombocytopenia were more common in CyA patients, whereas diarrhoea and other gastrointestinal adverse events were more common in TAC patients. The profile of AEs in transplantations with DGF was different from that in transplantations with immediate kidney function (Figure 1 in publication II).

5.5.2 MMF dose reductions

In 139 (34%) transplantations the MMF dose was reduced within the first 100 days. Among them, in 93 the MMF dose was reduced and in 46 it was discontinued. Of all dose reductions, 78% occurred in the first 3 weeks after transplantation. In 268 (66%) transplantations full MMF dosage was used throughout the period. As there were no previously agreed criteria for clinically important ALAT increase the MMF dose changes were made at the doctors' discretion, and so the level of ALAT at the time of MMF dose reduction varied greatly (mean 173 U/l, range 63 – 643 U/l)

Overall, 34% of the 407 transplantations examined in this analysis had at least one MMF dose reduction (Figure 5).

The most frequent cause of MMF dose reduction was ALAT increase (N: 90). Haematological abnormalities were the reason in 24 transplantations (leukopenia, 18; thrombocytopenia, 6; anaemia, 3), gastrointestinal symptoms in 15 cases and severe infection in 4 transplantations.

There were significantly more dose reductions in transplantations with CyA (40 %), compared to TAC (24 %), $p < 0.005$. Onset of graft function did not have an effect on the number or the timing of MMF dose reductions.

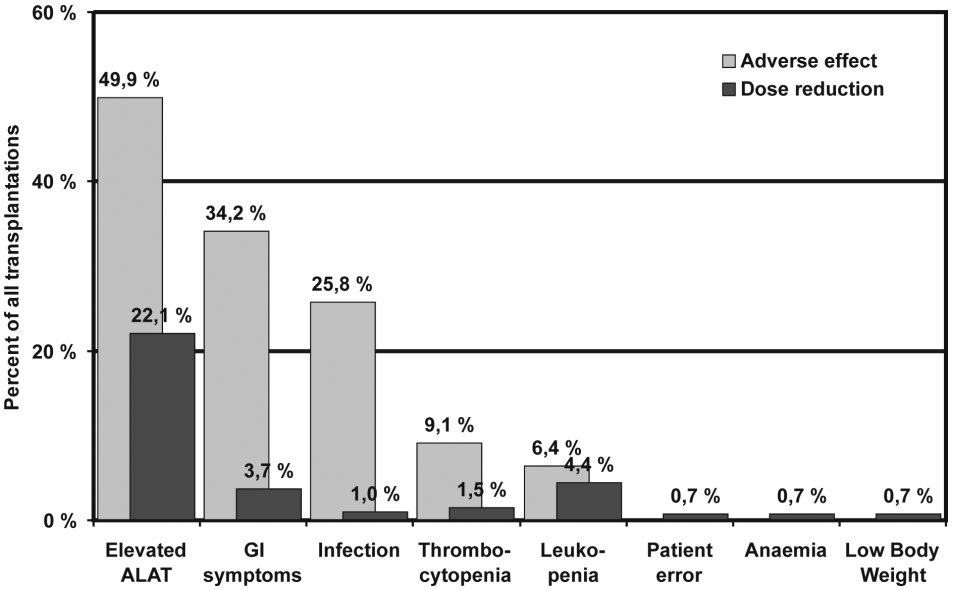

Figure 5. The proportions of adverse events and MMF dose reductions in 407 kidney transplantations

5.5.3 Impact of MMF dose reductions on transplantation outcome

Overall, 47 patients (12%) had acute rejection and the mean time to rejection was 22.6 days (range 4–99). The overall rejection rate in transplantations with a full dose MMF was 9% compared to 17% in transplantations with MMF-dose reductions (p=0.023)

As most MMF dose reductions occurred during the early post-transplantation period, transplantations were divided into two groups according to whether the MMF dose had been reduced or not by post-transplantation day 21, and rejections during the subsequent three-week period were analysed. Among TAC patients, 2.7% with full dose MMF had rejection during the following three week period, compared to none with dose reduction (N.S.) whereas in CyA-patients, the respective rates were 0.6% and 10% (p=0.0002).

At 3 and 6 months after transplantation there were no statistically significant differences either in the serum creatinine values or in the GFR between full MMF dose patients and reduced dose/discontinuation patients.

6. DISCUSSION

6.1 Deceased donor trends and impact of donor risk factors on transplantation outcome

Significant changes have occurred in the quality of our donor population during the last two decades, mostly in donor age. The proportion of elderly donors have both increased significantly. The relative number of female donors has increased gradually, perhaps due to the decreasing trend in high energy traumas and gunshot wounds as the causes of death in the male population. The number of donors with coronary artery disease or cardiopulmonary resuscitation was small, but showed a rising trend, while donor hypertension tripled during the study period. This trend is important as it has been demonstrated that kidney grafts from hypertensive donors develop significant morphological changes and deterioration of function in a relatively short time compared to grafts from normotensive donors (Pratschke, 2004). Incidence of smoking and alcohol consumption of donors at admission has also showen increase.

Many transplant centers have tried to solve the problem of organ shortage by accepting so-called "marginal donors" for transplantation. The definition of a marginal (or suboptimal) donor may vary among different transplant centers, it can mean a non–heart-beating, diabetic, or old donor. Until the early 1990s the list of contraindications for deceased kidney donation included hypertension, ventilator dependence longer than 7 days, signs of aspiration, age over 60 years, etc. Since then, most of these factors have become only relative contraindications or completely obsolete. Nevertheless, this has not been applied to acceptance of donors with a markedly elevated serum creatinine. Nor have our donors within the time periods of the present studies exceeded the 70-year age limit.

Concerning the completeness of the donor clinical data collection, we believe that reporting of the donor's medical history has been accurate. As hypertension, long stay on the ventilator, and cardiopulmonary resuscitation were earlier contraindications for transplantation, these data have been requested and recorded. In contrast, reporting of behavioral data, such as smoking habits and alcohol consumption, may have been less than perfect in the early transplantation period, especially when the organs were procured and the documentation was supplied by the local surgical teams.

We found a significant increase in delayed graft function among transplantations from hypertensive donors, a finding consistent with those of Carter and Lee. (Lee, 1998; Carter, 2000). When using ECD kidneys that nobody wanted, including kidneys from hypertensive, diabetic, and old donors, Lee et al observed a delay in the onset of diuresis, but claimed that at 1 year post-transplantation these kidneys were doing as well as those from the controls. In our study patients receiving transplants from hypertensive donors had substantially higher creatinine levels both at 3 weeks and 1 year after transplantation compared to patients receiving organs from non-hypertensive donors.

Increased donor age and cerebrovascular cause of death were significant risk factor for DGF and for higher 1-year serum creatinine. As both of these factors have been associated with the risk of developing chronic allograft nephropathy (Lietz, 2004), this trend might also predict poorer long-term results in the future. In multivariate analysis of our study only donor age and CMV status remained significant. The vanishing effect of donor age when deaths with a functioning graft were censored probably reflects our attempt to avoid extreme age mismatches between donors and recipients. We do not have, however, a special old-to-old program, as the primary criterion in our recipient selection has been good HLA match.

The impact of pretransplantation recipient comorbity has been measured in different ways (Jassal, 2005) and a link between increased comorbidity and reduced patient and graft survival has been suggested (Wu, 2005; Hernandez, 2005). Significance of donor comorbidity, however, has not been properly investigated, and, in particular, the association of donor comorbidity with baseline kidney histology and ultimately the transplant outcome has remained unclear. We studied the prognostic significance of an easily measurable parameter, the cumulative number of risk factors in this respect. The donor comorbidity (or risk) score obtained in this way was associated with graft function and survival and can be used in the future for assessment of organ donor quality. Our results agree with the earlier report of Loven et al., who found that graft function at one year was associated with the combined comorbidity score (Loven, 2003). There was also a trend to worsening of graft survival with an increasing number of risk factors. Machnicki at al. established several donor comorbidities as risk factors for graft loss, but did not specify their combined impact (Machnicki, 2009).

The trend towards a less optimal donor profile observed in this study can be accepted, as the expanding donor pool has not yet had an adverse effect on the outcome of kidney transplantation. All attempts should be tried to avoid additional injury to the graft, e.g., minimizing the length of CIT, avoiding nephrotoxic medications etc.

6.2 Influence of donor risk factors on baseline kidney morphology

Our study is one of the largest single-centre series of clinical and histological donor quality assessment. We found significant correlation between donor risk factors and morphological changes in the kidney. Donor age was the strongest predictor of damage in all histological compartments. We showed that the impact of donor age on graft outcome occurs through glomerulosclerosis but also through vascular and tubulointerstitial damage.

Hypertension predicted glomerular and vascular sclerosis in the donor kidney, but this negative effect on vessels was only seen in the untreated hypertension group. The detrimental effects of high blood pressure on the kidneys

appear to be averted by proper treatment. Our results confirmed the previous evidence of the influence of smoking on blood vessel lesions in chronic glomerulopathies (Lhotta, 2002) as well as in kidney transplants (Zitt, 2007). Surprisingly, a history of coronary artery disease or other atherosclerotic disease was not significantly associated with vasculopathy in the biopsies, which may be explained by the low prevalence of this pathology in our study population.

Proposed donor scoring systems generally include only cause of death, hypertension and diabetes from donor medical history as the risk factors with the strongest impact (Nyberg, 2001; Port, 2002; Schold, 2005). In this study we supplemented risk estimation with all available information from the donor medical history. Donors with several comorbidities are likely to have more severe histological changes in virtually all compartments of the kidney, expressed in GS, arteriolar hyalinosis, vascular intimal sclerosis and tubular atrophy. Increase in CADI score characterizes particularly well the number of pretransplant risk factors.

Finally we analysed the probability of a significant pathology in different donor groups, as the principles of taking donor biopsies are not identical. In young donors with traumatic brain death there were no biopsies with significant GS or with a high CADI score. A biopsy in this group of donors serves rather as a reference for possible follow-up biopsies after transplantation.

6.3 Predictive value of histological parameters or CADI score of donor kidney on post-transplant outcome

Most importantantly, this study confirmed the significance of baseline histology in donor assessment. We found that kidneys with >20 % GS were associated with worse graft function and survival. Particularly, a high percentage of GS negatively affected graft survival, although Bajwa et al. have recently shown that even lower levels of GS (> 5%) may be associated with impaired graft survival (Bajwa, 2007). Whether we should discard a donor kidney based on the degree of GS in the baseline biopsy is still subject to discussion. A 20% GS cutoff proposed by Gaber et al. has been used by many other authors as a donor quality criterion (Escofet, 2003). Several studies, however, have questioned this threshold (Pokorna, 2000; Lu, 2000). One of the reasons for this discrepancy may be the low incidence of significant GS in donor biopsies among most study populations. For example, the conclusion of Gaber et al was based on biopsies of only 8 kidneys. In our study ≥20 % GS was associated with significantly lower death censored graft survival at 5 years compared to recipients of kidneys with lower percentage of GS. Still, these kidneys could be considered an acceptable solution for patients with shorter life expectancy.

Arteriosclerosis was not associated with delayed graft function, nevertheless, vasculopathy (severe, in particularl) predicted worse long-term graft function.

The results of previous studies are controversial, some studies showing a negative impact of vasculopathy on the recovery of kidney function after transplantation (Matignon, 2008). The impact of vascular sclerosis on long-term results has, however, been demonstrated repeatedly by Pokorna (Pokorna, 2000), Kayler (Kayler, 2008) and others (Taub, 1994; Wang, 1998).

There is consensus about a classification system for grading kidney allograft pathology, but there are no generally accepted systems developed specifically to interpret donor biopsies. Several histological scoring schemes have been proposed for donor biopsies, e.g. Remuzzi score (Remuzzi, 1999), Total chronic Banff score (Snoeijs, 2008), Donor chronic damage score (Lopes, 2005)and Maryland aggregate pathology index (Munivenkatappa, 2008). These scores include more or less of the Banff components weighted in slightly different ways, e.g. in the scoring of GS percentage. After its introduction in 1992, CADI has been used routinely for post-transplantation follow-up biopsies at our center and was thus selected to evaluate donor biopsies in this study.

Despite some known weaknesses of the CADI score (Roberts, 2007), it has been shown to be a good predictor of graft outcome in the post-transplantation period (Yilmaz, 2003). As differences from other scoring systems are small and some of the additional components of CADI (interstitial inflammation and mesangial matrix increase) were practically always zero in our donor biopsies, use of some other scoring system would probably have led to similar results. We found that a CADI score >3 was associated with worse graft function and survival. This confirms the results of the recent report of Snoeijs et al. who were using the Remuzzi score and found significantly worse graft survival at a similar score level (Snoeijs, 2008). Our results show that CADI, when determined for donor kidneys before transplantation, is a prognostic marker for graft outcome.

It has been suggested that some of the ECD kidneys should be considered for dual kidney transplantation (Snanoudj, 2009). Although some of the donors in our study had significant histological changes and one fourth of the donors fulfilled the ECD criteria, the GFR of all these donors was in the normal range. Thus, it would have been pointless to proceed with dual kidney transplantations in these cases.

One of the strengths of our study is the long follow-up time. We followed graft function up to 3 years and survival up to 5 years, which is longer than in most previous studies. In our study all biopsies were reviewed by one pathologist, which avoided significant variability and low reproducibility between the results of different pathologists (Furness, 2003).

As to the effect of GS on graft outcome, there is no agreement on the minimum number of glomeruli necessary for a sample to be representative. The different minimum required number of glomeruli in the studies is variable, sampling error may partly explain conflicting results. We believe, however, that the sample size in our study was representative, as increasing the required number of glomeruli over 7 did not change the results of survival analysis, although it strengthened the statistical relationship.

6.4 Efficacy of early conversion to MMF in high risk patients and recipient related risk factors for graft survival in kidney transplant population

The primary goal of this study was to assess the efficacy of MMF treatment in patients with high immunological risk characterized by a high number of retransplantations, low HLA match and early acute rejections (Table 1 in publication I). Our results showed that treatment with MMF improved graft survival, compared with treatment with AZA, about 16% at 6 years. Better graft survival was observed despite the fact that the MMF group was characterized by a larger proportion of retransplantations and rejection episodes before switching from AZA to MMF. As it has recently been shown that second grafts have approximately 10 % lower five year survival than first grafts (Pour-Reza-Gholi, 2005), we could actually expect lower graft survival in the MMF group.

Acute rejection is still a significant risk factor for chronic allograft injury in our transplant population. According to our results, switching from AZA to MMF as rescue therapy after acute rejection can avoid the negative impact of rejection on long-term graft survival. This is consistent with previous studies where MMF, in addition to reducing the acute rejection rate, also improved the prognostic significance of these rejection episodes (Hazzan, 2004). One of the possible explanations may be that MMF prevents development of chronic allograft nephropathy irrespective of acute rejections. Nankivell et al have recently shown that MMF therapy is associated with reduced fibrosis in the glomerular, vascular and interstitial compartments, and with a delayed expression of CsA nephrotoxicity in comparison with AZA treatment (Nankivell, 2007).

One of the most important aspects of this study is relatively long follow-up time, while most studies dealing with survival differences between MMF and AZA treated patients, have shorter (1–4 years) follow-up times (Meier-Kriesche, 2001; Johnson, 2002; Hazzan, 2004; Meier-Kriesche, 2004; Shah, 2006). Our data demonstrate that survival advantage of MMF compared to AZA persists at least up to 6 years.

Cardiovascular risk factors, like systolic blood pressure, cholesterol level and CsA daily dose were less expressed in the MMF group compared to the AZA group one year after transplantation, although concomitant medication was not different for the groups. This supports the use of MMF as a way to reduce the risk of cardiovascular mortality which is the main cause of death after transplantation (Meier-Kriesche, 2003).

The main limitation of this study is the retrospective inclusion of patients, which may have created some selection bias for analysis. The MMF group, however, consisted of high-risk patients, who needed intensification of immunosuppression. Therefore the bias in our study population was actually against beneficial survival effect of MMF treatment.

Our results show that DGF significantly decreased and treatment with MMF (versus AZA) improved the kidney graft survival in the Estonian kidney transplant population. In univariate analysis, also donor age and hemodialysis slightly increased the risk of graft loss. DGF rate in our study was lower than usually reported (Feldman, 1996), which may by related to our notably short CITs. Keeping CIT as short as possible is certainly an option for improving results in a small population like Estonia as optimal HLA matching is not possible. Graft survival was better in recipients who were treated with MMF, despite their unfavourable immunological risk profile. The results of a recent study from Vienna (Kainz, 2009) support the results of our study. This is a very important issue considering the trend of continuous increase in the proportion of immunized and retransplantation patients in the Estonian waiting list.

The waiting list of kidney transplantation in our center is relatively small reflecting the size of our population (1.4 mln), therefore one of the main problems in allocation is low prospect for HLA matching. Analyses of large registry data have revealed relationship between HLA matching and graft survival that persists even in the era of modern immunosuppressive therapy (Terasaki, 2000). According to the data of Collaborative Transplant Study the difference in 3-year graft survival in transplantations with 0 and 6 HLA mismatches is 14 % (Opelz, 2001). Meier-Kriesche assessed separately MMF and AZA treated patients and found that use of MMF does not obviate the benefits of HLA matching, as improvement in 3 year graft survival was comparable for both groups (12 %) with full HLA match (Meier-Kriesche, 2001). Considering the poor HLA match in most transplantations of our study it is likely that these grafts are at higher immunological risk compared to those in many other centres. Nevertheless, this immunological risk did not lead to lower graft survival, which is consistent with studies reporting decreasing significance of HLA matching in last decades (Su, 2004).

The slightly increased risk associated with pretransplantation hemodialysis as compared to peritoneal dialysis has also been noted also earlier (Cancarini, 2006; Snyder, 2002; Van Biesen, 2000). Different explanations have been proposed for this phenomenon: more stable fluid status in PD patients (Rottembourg, 1993), higher risk of immune activation after hemodialysis session (Vanholder, 1999) and better biocompatibility of the peritoneal membrane versus dialysis membrane (Hakim, 1994).

Several other risk factors turned out to be nonsignificant in this study, including the comparatively high rejection rate. This supports the opinion that with proper management and more powerful immunosuppressive therapies we can largely eliminate the negative impact of acute rejection episodes on graft survival.

In conclusion, our study shows that MMF treatment has a positive effect on graft survival after kidney transplantation compared to AZA treatment in high-risk patients. Switching from AZA to MMF as rescue therapy after acute rejection prevents the negative prognostic implication of rejection episodes.

6.5 MMF intolerance and its impact on transplantation outcomes

One of the aims of this study was to describe the safety profile of MMF and to determine how the adverse events of MMF and dosing changes affect the early results of kidney transplantation. Although adverse events were observed in 3/4 of the patients, MMF dose reduction was needed more rarely (34 % of cases during half a year) than in studies of Knoll (59%) or Pelletier (70% during a year) (Pelletier, 2003; Knoll, 2003).

It was a surprising finding that elevation of liver transaminases was the most frequent adverse event in our series occurring in one half of the patients with dose reduction, and it was the most frequent cause of dose reduction. Hepatotoxicity has generally not been reported as a major cause of MMF dose change, which probably denotes that mild cases of liver dysfunction may be self-limiting. In this study more than half of the patients with elevated liver enzymes had no MMF dose change either. Most of them had only moderately elevated ALAT which returned to normal without dose changes.

The incidence of other adverse events was consistent with relevant data from earlier reports. One third of the patients had some gastrointestinal adverse event, the majority of which were mild and were conservatively treated. Only one-tenth of such events led to MMF dose reduction. Severe gastrointestinal events occurred in less than 1 % of the patients, which is even less than reported from US (Sollinger, 1995) and European trials (Pichlmayr, 1995).

Our results demonstrate that MMF associated adverse events depend on early posttransplantation graft function, occuring more frequently in recipients with DGF. This can be explained by the pharmacokinetic properties of MMF. Kaplan et al. have shown that the concentration and free fraction of mycophenolic acid (MPA), an active component of MMF, are elevated in patients with severe renal dysfunction (Kaplan, 1999). It is unclear, however, whether patients with severe renal insufficiency would need MMF dose adjustment (Kaplan, 1999). Patients with side effects could benefit from MPA measurement as pharmacokinetic studies have shown that low bioavailability of MPA, measured by area under the curve (AUC), is associated with higher incidence of acute rejections (Hale, 1998), whereas high MPA AUC values can increase the toxicity of MMF (Mourad, 2001; van Gelder, 1999). Although MPA is more easily measurable via trough concentration, it does not adequately reflect MPA AUC and is therefore not routinely used (Kuypers, 2003).

Unfortunately, at the time of transplantation of these patients, MPA measurement was not in routine use at our institution. In patients with high DGF risk, Novoa et al. suggested to use enteric-coated sodium mycophenolate in patients with high DGF risk, which may result in better gastrointestinal tolerability (Novoa, 2007). Eleven percent of the patients in their study, however, needed mycophenolic acid dose adjustment due to gastrointestinal adverse event, which is more than in our series with MMF.

There were significanly more gastrointestinal adverse events in MMF-TAC treated patients than in MMF-CyA treated patients in our study. The reason for this may be additive effect of both drugs, as gastrointestinal adverse events with TAC have been commonly reported as well (Yocum, 2004) (Yocum, 2004). The pharmacokinetic explanation is apparently augmentation of MPA levels in patients receiving MMF in combination with TAC as was documented by Zucker et al. (Zucker, 1997).

MMF dose reductions were associated with the rate of acute rejections. Patients with early MMF dose reduction during the first 3 weeks had a significant risk of developing acute rejection in subsequent 3 weeks (odds ratio 7.8, p=0.0013). This risk, however, depended on the calcineurin inhibitor used. In TAC patients dose reduction did not increase the subsequent rejection risk, whereas in CyA based therapy the dose reduction or withdrawal of MMF significantly increased the risk of acute rejection. This finding of our study is clinically important as in previous studies the association of MMF dose reduction with rejection rate has not been separately analysed in CyA and TAC patients (Knoll, 2003; Pelletier, 2003). Our results are consistent with studies that have shown a relationship between MMF dose and incidence of acute rejections in CyA treated patients (Sollinger, 1995; van Gelder, 1999). In patients treated with TAC it has been shown that a higher MMF dose is associated with higher toxicity without substantial improvement in efficacy (Squifflet, 2001). In CyA patients the inability to take the recommended MMF dose brought along an increased rejection risk with rejections occurring at a later time after transplantation than usually, thus necessitating prolonged close surveillance. In TAC patients no such risk was apparent and one might even ask whether concomitant maintenance immunosuppression with a full dose MMF in TAC patients actually renders them into a state of overimmunosuppression.

7. CONCLUSIONS

1. There was a trend toward negative changes in many donor qualities during the study period, like donor age, traumatic cause of death, hypertension, coronary artery disease and smoking incidence. Most of these factors influence early graft function; long-term graft survival was significantly affected by donor age and CMV serostatus. However, expanding the donor pool has not yet had a negative impact on the results of kidney transplantation. Multiple risk factors in a donor indicate poor graft outcome.
2. Donor age was the most significant factor affecting all single histological parameters and CADI score in donor biopsies. Cerebrovascular cause of death predicted vascular damage and higher CADI. Increase in number of concurrent donor risk factors is manifested by higher glomerulosclerosis and CADI.
3. Although originally created to describe post-transplantation changes in kidney grafts, pre-transplantation CADI of a donor kidney can predict long-term graft function and survival. Glomerulosclerosis is another significant marker for unfavourable transplant outcome. Other individual histological parameters, like arteriosclerosis, tubular atrophy and interstitial fibrosis, also predict graft function after transplantation.
4. MMF improves graft survival after kidney transplantation compared to AZA in high-risk patients. Converting immunosuppression from AZA to MMF after acute rejection prevents the negative prognostic implication of these episodes on graft survival. DGF and immunosuppressive treatment significantly influence the graft survival kidney transplantation population.
5. Overall, 1/3 of the transplantation patients in our study required at least one MMF dose reduction. The most frequent cause of this was hepatotoxicity, necessitating dose reduction in almost half of cases. Only a small proportion of other gastrointestinal adverse events actually needed MMF dose reduction. DGF increased the risk of occurrence of adverse events. In CyA patients the reduced MMF dose increased acute rejection risk, while TAC patients had no increased rejection risk despite MMF dose changes.

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SUMMARY IN ESTONIAN

Neerusiirdamine: uuring doonori riskifaktoritest ja mükofenalaat-mofetiilist

Neerusiirdamine on kaasajal parim ravimeetod terminaalse neerupuudulikkusega haigetele, kuna ta parandab elukvaliteeti, pikendab elulemust ja on odavam kui dialüüsravi. Kuigi lühiajaline neerusiiriku elulemus on oluliselt paranenud, ei ole pikaajalises elulemuses samaväärset nihet toimunud. Oluliselt on vähenenud äratõukereaktsioonid, mistõttu põhiliseks siiriku kaotuse põhjuseks on muutunud krooniline transplantaadi düsfunktsioon ja surm funktsioneeriva siirikuga. Seetõttu peab järjest enam tähelepanu peab pöörama ka mitte-immunoloogilistele teguritele, samas kui puuduvad uuringud Eestis siirdatud patsientide kaugtulemusi mõjutavatest teguritest.

Siirdamisjärgselt kasutatakse kõige enam kolmikravi kaltsineuriini inhibiitori, antiproliferatiivse preparaadi ja glükokortikoidiga. Kuigi mükofenolaatmofetiil (MMF) on tugevama immuunsuppressiivse toime tõttu azatiopriini paljudes keskustes välja vahetanud, pole veenvalt tõestada suudetud tema mõju kaugtulemustele. Eestis kasutati MMF-i esialgu empiiriliselt kõrge immunoloogilise riskiga patsientidel, samuti peale ägedat äratõuget, kuigi puudus piisav teaduslik tõestus sellise skeemi efektiivsusest. Nagu ka mitmete teiste ravimitega, on MMF-ga ilmnenud erinevaid kõrvaltoimeid, mis võivad viia ravi katkestamiseni või doosi langetamiseni. Ebaselge on kui palju tõstab ravi muutmine äratõuke riski ja halvendab sellega prognoosi.

Seoses kasvava ootelehega on üle maailma suundumus laiendada potensiaalsete doonorite ringi. Rahuldavate siirdamise tulemuste tagamiseks ja vajalike meetmete tarvitusele võtmiseks on oluline teada trende kadaveerses organdoonorluses. Järjest enam aktsepteeritakse siirdamiseks ka madalama kvaliteediga doonoreid, mistõttu on vajalik täpselt defineerida olulisemad siiriku prognoosi mõjutavad tegurid ja minimaalsed kvaliteedi nõuded. Kuigi doonori vanus on üks olulisemaid kvaliteeti mõjutavaid tegureid, ei ole see üksi piisav otsustamaks organi sobivuse üle. Haigusanamnees võib anda olulist lisateavet doonori kvaliteedi ja sobivuse kohta, mida senised hindamissüsteemid täielikult ära ei kasuta ja mille uurimine oli ka meie üheks töö eesmärgiks.

Lisaks anamneesile kasutatakse organi sobivuse hindamiseks, eriti kõrgema riskiga doonoritel, baasbiopsiat. Ebaselge on kui palju mõjutavad doonori riskitegurid ja kaasnevad haigused neeru histoloogilist leidu, samuti pole üheselt määratletud morfoloogilisi kvaliteedikriteeriume. CADI (Chronic Allograft Damage Index) skaalat, mis algselt töötati välja siirdamisjärgsete histoloogiliste muutuste klassifitseerimiseks, pole piisavalt uuritud baasbiopsiate hindamisel, mis oli seetõttu antud uuringu üheks eesmärgiks.

Töö eesmärgid

Töö üldeesmärgiks oli uurida neerusiiriku funktsiooni ja elulemust mõjutavaid tegurid ja võimalusi parandada kaugtulemusi.

Uurimistöö erieesmärgid olid järgmised:

1. Analüüsida trende organdoonorite kvaliteedinäitajates ja uurida doonoripoolsete riskifaktorite tähtsust siirdamise tulemustele.
2. Hinnata doonori riskifaktorite ja kaasnevate haiguste mõju doonorneeru morfoloogiale ja CADI väärtusele.
3. Uurida doonori baasbiopsia üksikute histoloogiliste parameetrite ja CADI skaala prognostilist väärtust siirdamise tulemuste hindamisel.
4. Uurida varase AZA-lt MMF-le ümbervahetamise efektiivsust kõrge äratõuke riskiga patsientide rühmas ja võrrelda neerusiiriku elulemust MMF ja AZA ravi saanud patsientidel. Selgitada retsipiendi poolsete tegurite mõju neerusiirdamise tulemustele.
5. Hinnata MMF ravi kõrvaltoimeid, neist tingitud doosi vähendamisi ja mõju äratõuke reaktsioonide sagedusele ning siiriku funktsioonile.

Materjal ja meetodid

Antud uuring koosnes neljast alauuringust, mis viidi läbi Tartu Ülikooli Kliinikus ja Helsinki Ülikooli Kliinikus. Tegemist oli retrospektiivsete kliiniliste uuringutega neerusiirdamistest aastatel 1996–2005. Tartus läbi viidud uuringus võrreldi MMF ja AZA ravi efektiivsust ja kaugtulemusi 137 patsiendil aastatel 1996–2001. Helsinkis läbi viidud kolm uuringut hõlmasid 407 – 2006 retsipiendi ja 481 – 1119 doonori andmeid, kes osaliselt uuringutes kattusid. Jälgimisaeg kõikus uuringutes 6 kuust kuni 6 aastani.

Uuring II hõlmas MMF ravi saanud retsipiente aastatel 1992–2003, uuring III ajusurmas doonoreid ja neilt saadud neerusiirikute tulemusi aastatel 1991–2003 ja uuring IV doonoreid kellelt oli võetud baasbiopsia aastatel 1995–2005 ja nende siirikute tulemusi.

Kliiniline informatsiooni kogumiseks doonorite, siirdamiste ja siirdamisjärgse ravi kohta vaadati läbi algmaterjalina vastava perioodi haiguslood, jälgimisandmed saadi Helsinki ja Tartu vastavatest andekogudest (Soome Neerusiirdamise Register ja Ootelehe andmekogu Tartus). Siiriku lõppeks loeti tagasipöördumist dialüüsravile, siiriku eemaldamist või surma töötava siirikuga. Äratõuke reaktsioon diagnoos põhines siiriku biopsial. Kõikides uuringutes sisestati andmed analüüsimiseks vastavasse arvutiandmebaasi. Baasbiopsiad doonorneerust vaadati uuesti läbi ühe patoloogi poolt ja hinnati Banffi klassifikatsiooni. CADI väärtus saab olla 0 kuni 18, olles interstitsiaalse põletiku, tubulaaratroofia, veresoonte inima skleroosi, interstitsiaalse skleroosi, mesangiumi maatriksi rohkenemise ja glomeruloskleroosi alaskooride summa (igaüks 0–3).

Järeldused

1. Uuritaval perioodil oli täheldatav negatiivne trend mitmetes doonori kvaliteedi näitajates, nagu doonori vanus, traumad surma põhjusena, hüpertensiooni, südame isheemiatõve ja suitsetamise esinemissagedus. Enamik nendest teguritest mõjutasid varajast siiriku funktsiooni; siiriku elulemust mõjutasid kõige enam doonori vanus ja CMV serostaatus. Doonorite ringi suurendamine seni olulist negatiivset mõju siirdamise tulemustele avaldanud. Paljude riskifaktoritega doonor on seotud siiski halvemate siirdamise tulemustega.
2. Doonori vanus oli olulisim doonorbiopsia histoloogilisi näitajaid ja CADI väärtust mõjutav tegur. Tserebrovaskulaarse surma korral esines doonorneerul enam veresoonte kahjustust ja kõrgem CADI punktisumma. Mitme samaaegse riskifaktori esinemine doonoril on seotud kõrgema glomerulaarskleroosi ja CADI summaga
3. Algselt siirdamisjärgsete muutuste kirjeldamiseks loodud CADI skaala sobib ka doonorneeru kvaliteedi hindamiseks, kuna doonori CADI väärtuse alusel saab ennustada siiriku pikaajalist funktsiooni ja elulemust. Glomerulaarskleroos on samuti seotud siiriku halvema prognoosiga. Siiriku funktsioon sõltub lisaks ka muutustest teistes histoloogilistes parameetrites nagu arteriioskleroos, tubulaaratroofia ja interstitsiaalne fibroos.
4. MMF parandab neerusiiriku elulemust võrreldes AZA-ga kõrge äratõuke riskiga patsientidel. AZA vahetamine MMF vastu immuunsuppressioonravis peale äratõuke reaktsiooni teket vähendab äratõuke episoodide negatiivset mõju siiriku elulemusele. Hilinenenud neeru käivitumine ja immuunsuppressiivne ravi olid kõige olulisemad siiriku elulemust mõjutavad tegurid.
5. Üks kolmandik patsientidest meie uuringus vajas vähemalt korra MMF doosi vähendamist. Kõige sagedasem põhjus selleks oli maksatoksilisus, mis viis doosi langetamisele ligi pooltel juhtudel. Ainult väike osa seedetrakti poolsetest kõrvalnähtudest vajas MMF doosi vähendamist. DGF suurendas kõrvaltoimete tekke riski. CyA saavatel patsientidel tõstis MMF doosi langetamine oluliselt äratõuke riski, samas kui Tac saavatel patsientidel äratõuke risk ei kasvanud.

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PUBLICATIONS

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Teaduslik tegevus

Peamised uurimisvaldkonnad:
- riskifaktorid neerusiirdamisel ja kaugtulemused Eestis, krooniline transplantaadi kahjustus.
- 24 teaduspublikatsiooni, sh. 9 ettekannet rahvusvahelistel konverentsidel

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