

Renal transplantation is also an option for patients over 70

Summary

Background. Renal transplantation is accepted as the best form of renal replacement therapy. Due to an ageing population there has been a growth in the number of elderly people with end stage renal disease in recent years, and the numbers are expected to increase further. In this article our aim is to present an overview of current knowledge on survival after renal transplantation in patients over the age of 70 compared with results for similar patients on dialysis.

Material and methods. The article is based on a systematic search of the literature in PubMed and experience from our own research.

Results. For patients who satisfy the established medical criteria, renal transplantation offers a higher survival rate than lifelong dialysis. The prognosis is best if the pre-transplant duration of dialysis is reduced.

Interpretation. Renal transplantation is a safe procedure for eligible elderly patients with end stage renal disease. Provided that organs are available, eligible elderly patients over the age of 70 should be offered renal transplantation.

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Patients with terminal chronic renal failure (stage 5) can be offered conservative medical treatment or active renal replacement therapy. Renal transplantation is accepted as the best alternative with the proviso that the patient is capable of tolerating surgery and the subsequent medical treatment (1, 2). When there is pronounced comorbidity, patients will in some cases only be offered conservative medical treatment aimed at delaying progression and relieving uraemia symptoms.

Traditionally most elderly patients are offered dialysis, and only a few are assessed with a view to renal transplantation. As a result of increasing life expectancy, the number of elderly patients who need renal replacement therapy has risen in both Norway and elsewhere in the Western world (3, 4). In the last 20 years a large number of renal transplantations to elderly recipients have been carried out in Norway. Hypertension and hypertensive nephrosclerosis were the cause of renal failure in 50 % of Norwegian patients over the age of 70 who commenced active renal replacement therapy with dialysis or transplantation in 2009 (4). The median age for the start of renal replacement

therapy in Norway increased from 53 in 1980 to 65 in 2009 (4). Many elderly people with chronic renal failure die of other causes before they reach the stage where they require active treatment (5). Nevertheless, the fastest-growing need for renal replacement therapy is found in this age group internationally (3, 6).

Following the first successful kidney transplant in Boston in 1954 (7) this operation has developed from experimental research to a safe, routine procedure. Increased immunological knowledge together with the development of new immunosuppressant drugs have led to a marked improvement of the results (8, 9). Today transplantation is regarded as considerably less costly than dialysis (10).

There are solid indications that eligible elderly patients can also benefit from renal transplantation, compared with continuing on dialysis (11–15), and an increasing proportion of elderly patients are placed on the waiting list for transplantation both in Europe and the US (6, 16). In 2011 a total of 17 % of patients on the Norwegian waiting list are over the age of 70.

It is vital that the patients who are accepted for renal transplantation are those who will derive most benefit. In Norway, potential transplantation candidates are assessed according to a template which is age-independent. The assessment aims at excluding serious cardiovascular disease as well as cancer and other comorbidity, including mental illness and dementia. In addition, conditions that entail an unacceptably high risk in connection with the transplantation or post-transplantation must be eliminated. The assessment takes place locally and is headed by the patient's consultant nephrologist. Final approval of the individual case must be given by the transplanta-

Key points

- Renal transplantation is a satisfactory treatment for eligible patients over the age of 70
- Pre-dialysis transplantation or transplantation after a short time on dialysis gives the best results
- Acute rejection episodes are associated with reduced patient survival for elderly recipients

tion community at Oslo University Hospital, Rikshospitalet. The current assessment form can be downloaded at www.nephro.no/skjema.html. The Charlson Comorbidity Index (CCI) can be used to describe comorbidity as a risk variable in patients who are to undergo a kidney transplant (17). However, this kind of index assessment is not routinely used in Norway.

Internationally there is a considerably larger number of patients on waiting lists than there are available organs (18, 19). This entails a long waiting period – often lasting many years. The median wait for the first renal transplantation within the Eurotransplant collaborative framework (Belgium, Luxembourg, the Netherlands, Slovenia, Germany and Austria) was 55 months in 2009 (19), while the corresponding wait in Norway was 7.5 months (4). A number of patients will die while they are waiting for transplantation to be offered (20), or their general state of health may become so weakened that they are removed from the waiting list on medical grounds (21).

Following renal transplantation two end-points are assessed: patient survival and graft survival. Patient survival is the time from the transplantation is carried out until the death of the patient, with or without a functioning graft. Graft survival is the time from when the transplantation takes place until the transplant ceases to function, either as a result of graft failure, or because the patient dies. As early as 1995 the Norwegian data on transplant patients over the age of 70 described a five-year survival rate for 74 % of the patients who received living donor kidneys as against 54 % for those who received deceased donor kidneys (22). No comparison was made for survival on dialysis. The most common causes of death for elderly kidney transplant recipients are infections related to immune-suppressive therapy and cardiovascular disease (23).

In this article we will present existing knowledge about survival after renal transplantation in patients over the age of 70, including a comparison with dialysis treatment. We will also discuss factors that can affect survival.

Material and methods

The article is based on our own research as well as a review of the literature that describes long-term survival in kidney transplant recipients over the age of 70. The literature has been identified through a systematic literature search on Medline using the Ovid search engine. In addition, reference lists from studies found in the search were reviewed, and specific searches were conducted in relevant journals devoted to renal disease, geriatrics and transplantation medicine.

In the systematic search of the literature the key words were the MeSH terms «kidney transplantation [Major]» and «aged». In addition, the articles were to be indexed with

Table 1 Articles from the period 1 January 2000 to 1 April 2011 that describe long-term survival (> 2 years) following renal transplantation in patients over 70 years of age

First author	Inclusion	Number	Design	Age (years)	Patient survival (%)			
					2 yrs	3 yrs	4 yrs	5 yrs
Huang, 2010 (27)	2000–08	6 103	Multi-centre	70–80	86			
Huang, 2010	2000–08	199	Multi-centre	≥ 80	73			
Heldal, 2010 (26)	2000–07	117 ¹	Single-centre	≥ 70		74		64
Heldal, 2010	1990–99	116 ¹	Single-centre	≥ 70		60		39
Heldal, 2009 (25)	1990–2005	354	Single-centre	≥ 70				53
Rao, 2007 (12)	1990–2004	2 438	Multi-centre	≥ 70			66	
Macrae, 2005 (13)	1994–2000	46 ²	Multi-centre	≥ 75				60
Macrae, 2005	1994–2000	171 ³	Multi-centre	≥ 75				40
Herrero, 2003 (24)	1990–2001	41	Single-centre	≥ 70	83	75		

¹ Only patients treated with dialysis prior to transplantation
² Living donor
³ Deceased donor

one of the following MeSH terms: «prognosis», «survival rate», «treatment outcome» or «kidney transplantation/mortality». The search was limited to human studies in English published between 1 January 2000 and 1 May 2011. Altogether 1,065 articles were found. The abstracts of the identified articles were read by Kristian Heldal. The studies that dealt with recipients over the age of 70 and that described patient survival of more than two years after the renal transplantation were included.

Results

Six of the studies identified in the systematic search fulfilled the inclusion criteria (12, 13, 24–27). These are presented in Table 1. Since 80 % of patients in this age group die with graft function intact (23), the difference between patient survival and graft survival is minor. Therefore separate numerical values for graft survival are not provided.

A substantial body of data from the United States Renal Data System (USRDS) was published in 2007, which included 5,667 pa-

tients over the age of 70 (12). All were accepted for renal transplantation. This article describes a significantly better survival rate for renal transplant patients than for patients who continued on dialysis, with a relative risk of 0.59 (0.53–0.65).

Norwegian results

In a body of material that included all recipients over the age of 70 with a transplant from either a living or deceased donor in the period between 1990 and 2005, a total of 53 % were still alive after five years (25). Several variables significantly associated with survival after transplantation were identified in the same material. These are listed in Table 2. Somewhat surprisingly, no correlation was found between the comorbidity described by CCI assessment and survival in patients over the age of 70. In contrast to younger patients, where acute rejection was only associated with reduced graft survival, early rejection in elderly patients was strongly associated with poor patient survival. In the Norwegian material, the fol-

Table 2 Significant variables associated with death-censored patient- and graft survival with functioning graft following a renal transplantation in patients over the age of 70. The following variables were included in the models: comorbidity (CCI), age and gender of the recipient, donor over 60 years of age, gender of donor, living or deceased donor, cytomegalovirus in donor and recipient, tissue-type mismatch, pre-transplantation time on dialysis, cold ischaemia time, delayed graft function, acute rejection during the first 90 days. Adapted from Heldal and co-workers (25)

	Hazard ratio (95% KI)
Patient survival	
Rejection during the first 90 days after transplantation	1.74 (1.34–2.25)
Time on dialysis pre-transplant (per month)	1.02 (1.01–1.03)
Donor over 60 years of age	1.52 (1.14–2.01)
Graft survival (censored)	
Delayed graft function	3.69 (2.01–6.79)
Donor's age ≥ 60 years	2.42 (1.30–4.49)
HLA antibodies detected in recipient	3.96 (1.38–11.37)

lowing variables were associated with the development of acute rejection incidents independently of the recipient's age: less potent immunosuppression (azathioprine versus mycophenolate mofetil), tissue-type mismatches for HLA-DR and HLA-A, donor over 60 years of age and the presence of antibodies against tissue-type molecules (HLA) in the recipient (25).

In 2000, a general strengthening of the Norwegian protocol for immunosuppressive treatment following renal transplantation was undertaken. This change led to a dramatic reduction of the acute rejection rate for all age groups, including patients over the age of 70. For those over 70, patient survival was also considerably improved, while the survival rate for patients who continued on dialysis remained unchanged (26).

Using a Cox multivariate hazard regression model with a time-dependent covariate, a comparison was made of survival on dialysis and survival after transplantation in patients over the age of 70 when they were placed on the waiting list for renal transplantation. The analysis did not show a higher survival outcome for transplantation in the period from 1990 to 1999. However, patients who commenced dialysis after 2000 and who later received a transplant had a 60% lower risk of dying in the observation period compared with those who continued on dialysis without being offered a kidney transplant (26). The estimated 5-year survival rate for patients over 70 who had received a transplant after 2000 was 64% with a median survival of > 6.7 years. The corresponding rate for those who remained on the waiting list was 33%, with a median survival of 3.1 years.

Discussion

Renal transplantation is a safe treatment for eligible elderly patients with end stage renal disease. When there is a lack of organs it is challenging to prioritize between older and younger patients on the waiting list. Often young patients, who potentially have many years to live ahead of them, will be selected. Consequently very few transplants are carried out internationally in which elderly patients receive a kidney from a deceased donor, even though there is no formal upper age limit (3).

It is essential that good routines are established for the selection of patients who are eligible for renal transplantation. There is no scientific documentation that supports the introduction of an upper age limit (27). An American study found that comorbidity described using CCI assessment at the time of the transplantation was associated with post-transplant survival in patients over the age of 60 (28), but there were no corresponding findings for patients in Norway over the age of 70 (25). The probable explanation is that the oldest patients accepted for transplantation are selected, eligible patients with low comorbidity.

There are no randomized studies in which survival on dialysis is compared with survival following transplantation in elderly patients. Therefore comparisons must be carried out using epidemiological methods. Such a comparison is only described in two of the studies identified (12, 26). To ensure the validity of these analyses, it is essential that the groups compared are as similar as possible.

In the Norwegian material no great differences in patient characteristics were found between those who received transplants and those who remained on the waiting list. Certainly there was a somewhat greater incidence of diabetic nephropathy among those who did not receive a transplant (9% as against 3%, $p < 0.05$), but apart from this, the groups were comparable (26). A large proportion had also received a transplant (81%). As a result of the method adopted in which a Cox regression analysis with a time-dependent covariate was carried out, transplant recipients were also included in the waiting list group up to the time of the transplantation, so that they also contributed to the survival time of this group.

The American data have been obtained from many centres across the whole of the US and thus reflect a number of different treatment protocols. Only 43% of the patients in this material finally received a transplant, and due to the long waiting time we must assume that those who received a transplant were a selected group with particularly good health. This complicates the interpretation of the results and the transfer value to Norwegian patients may be limited.

A special programme has been initiated as part of the Eurotransplant collaboration – Eurotransplant Senior Program (ESP) – in which kidneys from elderly donors are allocated to elderly recipients (16). This is described as giving very satisfactory results. In this way increased waiting times for younger patients on the waiting list can be avoided (29). An American register study also describes a similar system (30). However, the use of kidneys from older donors also increases the risk of rejection. This may be attributed to a stronger immune response because of tissue damage in the older organ, which in turn can trigger the immune system of the recipient (31). Increased rejection also has a negative impact on survival in the oldest patients (25). Nonetheless, an analysis of data from patients who received transplants at a period of time when there was a low frequency of rejection showed that kidneys from elderly donors did not present an increased risk of death (32). Adequate immunosuppressive treatment and better understanding of pharmacokinetic principles in elderly recipients can thus reduce the risk of using a kidney from elderly donors.

The optimal immunosuppressive treatment for elderly patients following renal transplantation is not as yet clarified. Since

there is a lower incidence of rejection in elderly patients, it has been asserted that they may derive benefit from a milder immunosuppressive regime (33). On the other hand, a clearly higher survival rate and reduction of rejection frequency following intensification of treatment have been described (26). The decisive factor is the provision of sufficient immunosuppressive treatment to avoid rejection while ensuring that the treatment is not so intense as to increase the danger of infection. Often it is the anti-rejection treatment itself that leads to serious infections.

Since 2007, everyone over the age of 50 who has received a kidney transplant at Oslo University Hospital, Rikshospitalet has received induction therapy with interleukin 2-receptor antagonist in addition to prednisolone, cyclosporine A and mycophenolate mofetil. An assessment is now underway to determine whether this change causes a higher survival rate as a result of fewer rejections, or whether it will lead to higher mortality because of more infections.

The Norwegian results show that reduced time on dialysis is associated with improved survival after renal transplantation in patients over the age of 70 (Table 2), while this has not been consistently found in younger patients (25). It is therefore very important to identify and start assessment of elderly patients who are potential candidates for renal transplantation at an early stage. Ideally, the patient should receive a transplant *before* the need for dialysis is established or shortly after starting dialysis. The use of living donors gives a greater opportunity to achieve this, since in practice there is no waiting time when a living donor is accepted as a donor.

Conclusion

Renal transplantation is a safe and satisfactory treatment for patients with end stage renal disease – also for people over the age of 70. The patient must fulfill the medical criteria for acceptance for transplantation. Ideally, the patient should receive a transplant before the commencement of dialysis or as soon as possible after starting dialysis. Following transplantation, every attempt should be made to avoid acute rejection episodes or serious infections.

Work on the article has been carried out with the help of funding from the South-Eastern Norway Regional Health Authority and Telemark Hospital.

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Conflicts of interest: None declared

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Received 9 December 2010, first revision submitted 16 February 2011, approved 23 June 2011.

Medical editor Lars Frich.