

Sickle Cell and Renal Transplant: A National Survey and Literature Review

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Abstract

Sickle cell disease is an inherited, structural hemoglobin defect with multisystemic sequelae including renal failure. Patients with sickle cell disease are thought to benefit from renal transplant, but the long-term outcomes in such patients are unclear and have not been supported by any large prospective studies. Similarly, the renal morbidity and outcome after transplant in patients with sickle cell trait is also unclear.

There is little evidence concerning living donation in donors with sickle cell disease or sickle cell trait, either for the donor health or for the graft outcome, and there are no United Kingdom guidelines. The aim of this study is to review the evidence surrounding renal transplant in recipients and donors with sickle syndromes and to determine the attitudes and current practices of United Kingdom transplant centers to performing such operations.

Key words: *Sickle cell disease, Sickle cell trait, Renal transplant, Donor nephrectomy, Living donation*

Introduction

Sickle syndromes are inherited structural hemoglobin defects resulting from a substitution of valine for glutamine at the sixth codon of the β -globin chain, forming sickle cell hemoglobin.

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Acknowledgements: The authors declare that they did not receive any grants or financial support to produce this work.

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Experimental and Clinical Transplantation (2012) 1: 1-7

Where this abnormal gene is inherited in a homozygous manner, patients are described as having sickle cell disease (SCD). Patients that inherit only 1 faulty gene (heterozygous) are commonly described as having sickle cell trait (SCT). While SCT and SCD are most prevalent in populations originating from sub-Saharan Africa, they are also found in the Indian subcontinent, the Middle East, and Southern Europe.

Although anemia and sickle crises are more familiar manifestations of sickle cell disease, renal disease is common. End-stage renal failure (ESRF) is a feature of SCD and as in other dialysis-dependent populations, patients benefit from renal transplant. Live-donor transplant programs mean that family members, among others, may be approached as potential donor candidates. With the genetic inheritance of sickle syndromes, related donors themselves have a high chance of having sickle syndromes. The implications of using a sickle trait kidney as a donor organ are currently unclear.

The incidence among the black population in America has been reported at 0.25% for SCD and 8% for SCT.^{1, 2} Sickle cell nephropathy (SCN) can be difficult to confirm on biopsy and is often a diagnosis of exclusion.³ The reported incidence of ESRF in patients with sickle cell disease or trait varies widely. Based on the US Renal Data System, Abbott and associates reported that SCN was the causative factor for 0.11% of all patients initiating dialysis between 1992-1997.⁴ Another study by Warady found that children with SCD account for 0.5% of the dialysis population and 0.2% of patients on the North American Pediatric Renal Transplant Cooperative Study.⁵

Abbott found that patients with SCN are not only less likely to be placed on the transplant list, but those that were placed on the list were also less likely to undergo transplant RR0.38 (95% CI 0.24-0.60).⁴

Patients with SCN have a poor prognosis and were at increased risk of mortality compared to ESRF from other causes RR1.52 (95% CI 1.27-1.82) independent of age, race, sex, and comorbidities.

Despite the relative high prevalence of ESRF among sickle cell patients, there is a paucity of information surrounding renal transplant in such patients. To our knowledge, there are 4 studies detailing the outcomes for patients with sickle syndromes receiving transplants involving more than 10 patients.⁶⁻⁹ There are also several smaller series and case reports.^{5, 10-14}

The aim of this study is to review the literature regarding renal transplant and donor nephrectomy in patients with SCD and SCT to aid transplant centers as to how best manage these patients. Additionally, we undertook a survey to assess the attitudes and practices of UK transplant centers regarding living donation and sickle cell hemoglobinopathy.

Materials and Methods

We performed a literature review on PubMed using the search criteria "sickle cell," "nephropathy," "renal failure," and "transplant." All papers in English (1970-2010) were assessed for suitability and relevant papers reviewed in full (Table).

Additionally, we carried out an e-mail survey of 13 UK transplant centers regarding their practice using sickle trait candidates as live donors. Specific questions were focused upon the use of routine screening for sickle cell trait in potential donors and whether patients with the sickle cell trait would be considered for living donation. Approval by the local ethics committee was not necessary in this study as it did not involve a trial or experimental study.

Transplant in sickle cell disease

The largest published study by Scheinman⁶ identified 1656 patients with SCN and sickle cell disease using the US Renal Data System combined with hospitalization codes. Of these, 237 patients underwent transplant and 1419 did not receive a kidney allograft. Patients with SCD who did not receive an allograft had a dismal prognosis with a survival rate of 14% at 10 years. By comparison, the survival rate for patients with SCD who did receive transplant was 56% at 10 years. While the survival

for transplanted patients with SCD was less favorable than for African American patients as a whole, this was not significant when age-matched controls were used. For the 53 SCD patients who received a transplant after 1991, (and the widespread use of modern CNI immunosuppression regimens) the projected survival was 67% at 10 years compared with 83% in the non-SCD African American cohort.

Ojo and associates⁷ published another large series of sickle cell patients undergoing transplant. They compared an age-matched group of 82 African American transplant recipients with SCN with similar transplant recipients with ESRF of other causes. The mean age at time of transplant for SCD patients was 31 years. There was a similar incidence of delayed graft function (26% vs 29%; $P = .19$), creatinine on discharge (265.20 $\mu\text{mol/L}$ vs 238.68 $\mu\text{mol/L}$; $P = .42$), and 1-year deceased donor graft survival (78% vs 77%; $P = .82$) in the 2 groups. However, for live-donor recipients, the 1-year graft survival was only 61% compared to 86% in other ESRF recipients ($P = .013$). The study did not reveal whether the donors for the living donation group also had SCD or SCT. The 3-year graft survival for the sickle cell group was also significantly worse (48% vs 60%; $P = .0002$). The sickle group also had poorer patient survival with 1- and 3-year survival rates of 78% and 59% compared to 90% and 81% in their matched counterparts.

Chatterjee published the results of 2 surveys of US transplant centers.^{8, 15} In the 1987 study, only 20 of the responding 110 centers had experience with transplant in patients with SCD or SCT.⁸ The earlier 1980 study included 10 transplants on 9 patients with SCD.¹⁵ The 1-year graft and patient survival were 80% and 100%. Eight of the 10 grafts used were from deceased donors with 1-year graft and patient survival figures of 75% and 100%. Both patients with SCD undergoing live-related transplant were alive with functioning grafts after a year. Sickle cell crises occurred in 7 of 9 patients with SCD. The study concluded that short-term survival of transplant patients with SCD or SCT was similar to the nonsickle recipient population.¹⁵

Bleyer and associates⁹ reported patient and graft survival in sickle cell transplant patients based on the United Network for Organ Sharing (UNOS) registry from 1987 to 1996. Patients were included that had SCN denoted as their cause of renal failure. They found the 1- and 3-year patient survival for

Table 1. Outcomes for included studies.

| Study | Group | No. | Date | Population | 1-y graft survival | Long-term graft survival | 1-y pt survival | Long-term pt survival | Painful crises |
|---------------------------|-----------------------------|-------------|------------|--------------------------------------|---|--|---------------------------------------|--|-------------------------|
| Scheinman ⁶ | SCD transplanted | 153 | Up to 2000 | US Renal Data System | | | | 56% at 10 y | |
| | SCD transplanted post-1991 | 53 | 1991-2000 | | | | | 67% projected at 7 y | |
| | SCD not transplanted | 133 | Up to 2000 | | | | | 14% at 10 y | |
| Ojo ⁷ | Overall (81 SCD) | 82 | 1984-1996 | US Renal Data system + UNOS registry | | | 78% (90% in control group; P = .0001) | 59% at 3 y (81% in control group; P = .0001) | |
| | Deceased donor | 69 | | | 78% (77% in control group; P = .82) | 48% at 3 y (60% in control group; P = .0002) | | | |
| | Living donor | 13 | | | 61% (86% in control group; P = .013) | | | | |
| Bleyer et al ⁹ | SCD | | 1987-1996 | UNOS registry | 82.5% n=49 | 53.8% at 3 y n=23 | 90.5% n=54 | 75.0% at 3 y n=30 | |
| Chatterjee ¹⁵ | SCD | 10 (9 pts) | Up to 1979 | US National Questionnaire | 80% (8/10) | | 100% (10/10) | | 7/9 patients |
| | SCT | 24 (21 pts) | | | 62.5% (15/24) | | 83.3% (20/24) | 1/21 patients | |
| | Live related SCT | 7 | | | 71% (5/7) | | 86% (6/7) | | |
| | Live related SCD | 2 | | | 100% (2/2) | | 100% (2/2) | | |
| | Deceased donor SCT | 17 | | | 59% (10/17) | | 82% (14/17) | | |
| | Deceased donor SCD | 8 | | | 75% (6/8) | | 100% (8/8) | | |
| Chatterjee ⁸ | 13 SCD, 27 SCT | 45 (40 pts) | Up to 1984 | US National Questionnaire | 82% live related (9/11) 62% deceased donor (21/34) | | 87.5% (36/40) | | 11/13 patients with SCD |
| Warady et al ⁵ | 7 SCD, 1 SC-other, 1 S-thal | 9 | 1989-1995 | NAPRTCS database | 89% ± 11% | 71% ± 18% at 2 y | | | |
| Barber ¹⁰ | 6 SCD, 1 SCT, 1 S-thal | 8 | 1968-1986 | Case series Birmingham, US | 25% (2/8) vs 57% in control group | 12.5% at 18 mo | 75% (6/8) | | 6/8 patients |
| Montgomery ¹¹ | 3 SCD, 1 SC-other, 1 SCT | 5 | 1968-1993 | Case series Baltimore, US | 100% (4/4) | 100% at 3 y (4/4) | 100% (4/4) | 100% at 3 y (4/4) | 4/5 patients |

Abbreviations: NAPRTCS, North American Pediatric Renal Transplant Cooperative Study; S-thal, sickle thalassemia; SC, sickle cell; SCD, sickle cell disease; SCT, sickle cell trait; UNOS, United Network for Organ Sharing

transplant recipients to be 90.5% (n=54) and 75.0% (n=30). The figures for graft survival were 82.5% (n=49) and 53.8% (n=23) at 1 and 3 years.

Barber and associates¹⁰ reported less encouraging results based on an 18-year experience at their US center. In the 8 patients transplanted patients in their study (6 SCD, 1 SCT, 1 sickle thalassaemia), the graft survival at 1 year was only 25%, compared to 57% in the nonsickle African American population. There was only 1 functioning graft after 18 months (12.5%). Sickle crises occurred in 6 of the 8 patients after transplant, and 4 grafts were lost owing to sickling (between 3 days and 5 months after transplant). In 2 patients, crises were fatal. Other than perioperative blood transfusions, there is no mention of any other precautionary perioperative measures taken in these patients.¹⁰

Warady and Sullivan⁵ published the outcome for 9 patients on the pediatric register that underwent transplant. The mean age at time of operation was 16 ± 1.6 years. They reported good graft survival rates of 89% and 71% at 1 and 2 years. For the 3 patients whose grafts eventually failed, 1 had acute rejection, 1 died from unrelated causes, and 1 had chronic rejection and subsequently disease recurrence in 2 separate grafts.

Montgomery and associates¹¹ published their 25-year experience of 5 transplanted patients with SCN with 100% 1-year graft and patient survival. The authors reported a high incidence of severe painful crises after transplant in patients with SCD, supporting the findings of Chatterjee^{8, 15} and Barber.¹⁰

There are no randomized trials comparing methods of peri- and/or intraoperative management

for recipients with SCD. Brennan and associates¹⁶ proposed a protocol after a successful living-unrelated transplant at their center. They suggest preoperative transfusion until sickle cell preparation is negative, use of antithymocyte globulin on induction, and use of hydroxyurea in preference of azathioprine with the dual purpose of immunosuppression and stimulation of fetal hemoglobin.¹⁶ In a review by Sheinman,¹⁷ warming the graft with saline at 37°C, along with infusion of dopamine at 4 µg/kg/min during and after transplant, is advocated. Other suggestions include extra intravenous fluid to try to decrease blood viscosity, supplemental oxygen and recombinant erythropoietin until auto-production is sufficient. For patients who develop sickle crises, IV fluid and partial exchange transfusions, also have been suggested.⁸

Of the papers reviewed, there was a high reported incidence of painful sickle crises following transplant,^{8, 11, 15} thought to be the result of increased blood viscosity secondary to a functioning allograft. Several authors have reported acute allograft loss owing to sickling.^{10, 18} After transplant, patients with SCD are at higher risk of thromboembolic events such as deep vein thrombosis and renovascular thrombosis.¹⁹ There are several reports of recurrent SCN in a transplanted kidney. However, recurrence is thought to be a delayed phenomenon occurring many years after transplant.²⁰

Many patients with SCD require multiple blood transfusions and remain profoundly anemic despite large doses of erythropoietin. Breen and Macdougall²¹ reported 3 cases of patients with erythropoietin-resistant anemia whose need for transfusions decreased dramatically after transplant. Two of the patients had painful crises after transplant and were commenced on hydroxyurea. However, this resulted in thrombocytopenia in 1 patient and was therefore stopped.

At present, there are no UK guidelines concerning renal transplant in patients with SCD. Published guidelines by the Canadian Society of Transplantation state that renal transplant candidates with sickle cell disease should be considered for renal transplant if the systemic disease is not severe.²²

There are only 6 recorded cases of renal transplant performed in the UK in patients with sickle cell disease or trait according to UK transplant records, with a further 3 patients on the waiting list. However,

this is almost certainly an underestimation of the actual number as a result of incomplete disease coding.

Our center currently performs 180 renal transplants per year and has a wide catchment area with a large proportion of ethnic minorities. Despite encountering many patients with sickle cell disease and many more with sickle cell trait, we can only recall 4 patients in the past 10 years with SCD that received a renal allograft.

Transplant in sickle cell trait

Sickle cell trait was thought to be an extremely uncommon cause of ESRF. However, this has been questioned by a recent paper by Derebail and associates,² in which the incidence of SCT in the African American dialysis population was found to be twice that of the nondialysis African American population. There are few published studies regarding transplant in patients with SCT.

Chatterjee reported the graft and survival outcomes for 24 transplants performed in 21 patients with SCT.¹⁵ The 1-year graft and patient survival rates were 62.5% and 83.3%, which was worse than the survival rates for patients with SCD of 75% and 100%. For the 7 patients undergoing live-transplants, five (71%) were functioning at 1 year. For the 17 deceased-donor transplants, 10 (59%) were functioning at 1 year. Only 1 of these 21 patients experienced painful crises after transplant.

Donor nephrectomy in sickle cell trait and sickle cell disease

United Kingdom guidelines published by the British Transplant Society in 2011 state that potential donors should be screened for sickle cell trait "where indicated."²³ One would assume that this test would be "indicated" at a minimum in all patients of African descent and those with positive family history. These guidelines suggest that sickle cell disease should be an absolute contraindication to living donation.

Reese and associates²⁴ carried out a US questionnaire-based study and found that 113 of 137 centers (83%) had no policy to screen donors for the sickle trait. Thirty-nine of 105 centers reported excluding potential donors with SCT always or most of the time.

We performed a similar questionnaire-based survey of 13 UK transplant centers with a response

rate of 10 of 13 (77%). Of the units that responded, only 20% had a formal policy to screen potential donors for SCT, although all centers would consider using a graft from a donor with SCT. We found that most units had limited experience with sickle syndromes, with no set policy concerning screening for sickle donors, but would use a sickle trait organ for donation.

While there is no evidence that patients with SCT who undergo nephrectomy have a worse renal outcome than those that do not, SCT is associated with renal dysfunction. The degree of renal involvement is related to the percentage of hemoglobin in the patient with the sickle cell trait and renal manifestations are less severe than in SCD. Hematuria and impaired urinary concentration are the most-common signs of renal involvement, although increased urinary tract infections may be associated. Renal medullary carcinoma is a tumor seen almost exclusively in sickle cell trait patients. Although rare, the tumor is aggressive with a poor prognosis and is largely seen in young patients (less than 20 years old) with SCT. It is not known whether the renal graft from a donor with SCT performs as well as a kidney from a nonsickle donor. Our unit screens all potential donors of African descent for sickle syndromes and does consider patients with SCT as donors. There is limited information concerning live-related donation in donors that have SCD. Given the higher incidence of renal dysfunction and other comorbidities that occur with SCD, our center would not consider such patients for live donation.

Discussion

Patients with SCN are less likely to undergo transplant compared to patients with other causes of ESRF. The explanation for this is likely to be multifactorial. There is a shortage of Afro-Caribbean donors; reducing the availability of HLA-matched deceased-donor organs. Many patients with sickle cell disease require repeated blood transfusions resulting in high panel reactive antibody percentage or HLA antibodies and struggle to find a matched kidney. Patients with SCD or SCT who have developed end-organ damage also have advanced disease, and many are unsuitable to undergo transplant owing to cardiovascular and other forms of comorbidity. Live-related transplant is also

hindered by the hereditary nature of the condition, thereby limiting donor pool. Worldwide, sickle syndromes are more prevalent in areas with limited access to transplant and therefore, globally, there is relatively little experience in transplant among these patients.

The number of transplanted patients with SCD or SCT is likely to have been grossly under reported. Most studies are retrospective and registry-based and have included only patients with SCN designated as their cause of ESRF (this is not specifically coded for in UK transplant databases). However, there will be many more patients, particularly those with SCT, who have renal failure secondary to other causes and would not have been included. Furthermore, SCN is often difficult to diagnose, further contributing to disease under-representation.

As there are so few published series of transplant in sickle syndromes, it would be useful to combine the results from different studies to determine the overall graft and patient survival results for a much larger cohort. However, we have not done this, as the vast majority of the published studies are from the United States with patients derived from various registry systems. There is likely to be considerable overlap between studies and any single patient may have been included in multiple studies. Furthermore, to increase sample size, most studies span a wide time, during which management, and graft and patient survival, have improved dramatically, most notably with the advent of more effective immunosuppressant regimens.

Clearly, the 1-year graft survival figures presented in this report are well short of today's acceptable levels of > 95% for live-donor transplant. However, in all of the series, apart from that reported by Barber and associates,¹⁰ the 1-year graft survival was probably acceptable for the era in which they were performed. While the 25% survival in Barber's study is of some concern, there were only 8 patients in this retrospective study, commenced in 1968. Four patients lost their graft owing to sickling and the comparative graft survival was only 57% in the nonsickle population.

While there is reasonable evidence to support transplant in the sickle population, it must be performed with the knowledge that long-term graft and patient survival appears to be poorer than for other causes of ESRF but is greatly superior to the

prognosis of such patients on dialysis alone. In addition, there is the potential improvement in the patient's quality of life. Concern exists regarding the adverse effects of sickling in the perioperative and postoperative period and may partially explain poorer survival rates. Careful management of these patients is required to minimize any such effects.

A proposed surgical approach for transplant in the sickle patient is as follows:

1. Preoperative transfusions until the HbS percentage is less than 20 (or exchange transfusion where necessary). For patients undergoing living transplant, we would commence this 2 weeks before the transplant date.
2. Recipient preoxygenation with 40% O₂, continued for 48 hours after the operation.
3. During back bench preparation of either the living- or deceased-donor graft, the kidney is cold perfused in the normal fashion, and a surgical clip placed over the gonadal vein and is not ligated.
4. Before completion of the arterial anastomosis, 37°C saline is infused through the renal artery and vented through the gonadal vein. Once the vented solution feels sufficiently warmed, the arterial anastomosis completed, and 200 mL of recipient blood is vented in the same fashion and discarded followed by ligation of the gonadal vein.
5. Postoperative input from the surgical, nephrology, and hematology teams is required.
6. Immunosuppression based on current unit guidelines of tacrolimus, mycophenolate mofetil, and prednisolone with basiliximab on induction and day 4 in ABO compatible allografts.

This protocol has been used successfully and forms the basis of our current practice.

Conclusions

This literature review suggests that patients with sickle cell disease are at risk of developing SCN, and such patients have significant comorbid disease, and are a high-risk population. The risk of developing ESRF secondary to sickle cell trait is less clear. Renal transplant in patients with SCN does confer a survival benefit and should be encouraged. The controlled environment of live donation may confer increased benefits for this population group. There is little evidence and few guidelines relating to

performing donor nephrectomy in patients with sickle cell disease or trait. Despite this, most transplant centers, including ours, would be happy to proceed with donor nephrectomy in patients with SCT but not SCD, and such a pragmatic approach seems reasonable. A more rigorous screening process must be adopted to identify potential sickle cell donors to optimize the outcome for both organ donors and recipients.

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