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The impact of skin disease following renal transplantation on quality of life

F.J. Moloney, S. Keane, P. O'Kelly,* P.J. Conlon* and G.M. Murphy

*Departments of Dermatology and *Nephrology, Beaumont Hospital, Dublin 9, Ireland*

Correspondence
Dr Fergal J Moloney.
E-mail: fergalmoloney@eircom.net

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Summary

Background The immunosuppressive therapy a patient requires to sustain a functioning renal allograft in the long term is associated with various skin complications. While quality of life (QoL) after renal transplantation has been studied, no publications document the effect of post-transplant dermatological complications on QoL.

Objectives The objective of the study was to document the prevalence of the skin diseases that commonly occur in association with post-transplant immunosuppression. A general dermatological quality of life questionnaire, the Dermatology Life Quality Index (DLQI), was used to assess the QoL effect of these cutaneous complications. The study was designed to examine further the impact of age, sex, duration since transplant and immunosuppressive regimen on the DLQI score of renal transplant recipients (RTR).

Methods One hundred and seventy-three RTR completed the DLQI, were interviewed and examined for evidence of common post-transplant skin diseases.

Results Sixteen per cent of RTR had DLQI scores >6, reflecting a significant impact on their QoL. Dry skin, itch, hypertrichosis, sebaceous gland hyperplasia, acne, genital warts and a history of >4 herpes simplex virus type 1 infections in the past year were all found to have a significant impact on the quality of life ($P < 0{\cdot}05$). Multivariate analysis revealed that the greatest impact on QoL was in RTR who were younger, female and with multiple skin problems ($P < 0{\cdot}05$).

Conclusions The dermatological complications of immunosuppressive therapy are common in RTR and can significantly impair QoL in certain individuals. Visible, infectious and cosmetic skin problems had most impact on QoL while a history of skin cancer had a lesser impact. Early dermatological referral and careful choice of immunosuppression may enhance the QoL, particularly in young and female RTR.

Recent decades have brought steady improvements in the duration of patient and graft survival after renal transplantation; however, with improved survival comes increased comorbidity related to treatment. Cutaneous side-effects are particularly common with post-transplant immunosuppressive medication.[1] Eighty-five per cent of renal transplant recipients (RTR) have viral warts at 5 years after the transplant[2] while the cumulative incidence of skin cancer ranges from 5% to 25% at 10 years' post-transplant.[3] There have been no studies to date to evaluate the impact of cutaneous complications on the quality of life (QoL) after transplantation.

In recent years the assessment of treatments has come to include not only survival, but also the impact of disease on patients' perception of QoL. It is widely recognized that in comparison with the QoL of patients maintained on dialysis treatment, the QoL can improve dramatically after successful renal transplantation.[4] Three quarters of RTR are capable of resuming work compared with 25% of patients on haemodialysis and 59% of patients on peritoneal dialysis.[5] Post-transplant QoL studies, however, have not been extended to assess the many skin complications associated with maintaining a functioning renal allograft in the long term. Acne,[6] alopecia,[7] gingival hyperplasia,[8] skin cancer[9] and hirsutism[10] commonly occur after a transplant. These problems have been shown to have a significant impact on QoL in the non-transplanted population. Female and younger patient subgroups register the greatest impact on their QoL scores in a number of these studies. If this were true in the transplant population it could contribute to the poor compliance with immunosuppressant

regimens, which is a major cause of graft failure in young people.[11]

In this study, a general dermatological quality of life questionnaire, the Dermatology Life Quality Index (DLQI), was used in order to assess the impact of skin disease following renal transplantation. The study was designed to examine the effect of age, sex, duration since transplant, immunosuppressive regimens and common post-transplant skin complications on the DLQI score of RTR.

Methods

The DLQI developed by Finlay and Khan provides a simple practical scoring system for assessing the impact of skin disease.[12] It has to date been validated for over 100 dermatological problems including eczema, acne, psoriasis and most of the common skin diseases encountered in the follow-up of RTR. It consists of 10 questions, each with four possible answers scored from 0 (not at all) to 3 (very much). The higher the overall score, the more quality of life is impaired. The uncomplicated questionnaire format ensures a high rate of accurate completion.

The study was carried out over one calendar year from July 2003 in Beaumont Hospital, the National Renal Transplant Centre in Ireland. All RTR over 16 years of age attending the renal and dermatology outpatient departments were invited to complete the DLQI questionnaire. Data was collected on patient skin type according to Fitzpatrick's standard criteria, age and sex. Duration since transplant, immunosuppressive regimen at the time of interview, and personal or family history of skin cancer were also recorded. F.J.M. interviewed each patient and examined them for evidence of any of the dermatological complications that occur after transplantation and that were felt likely to have an impact on QoL. Evidence of hypertrichosis, dry skin, acne, sebaceous gland hyperplasia, steroid ecchymoses, dilated arteriovenous fistula on the forearm, viral warts, genital warts, skin cancer and visible scarring from surgery were all documented. Patients were asked if their skin itched every day or if they had had four or more herpes simplex virus type 1 infections in the past year. Medical records and histology reports were examined for details of previous skin cancer.

QoL scores were totalled and separated for the purposes of analysis into four groups: with no effect (DLQI = 0), small effect (DLQI 1–5), moderate effect (DLQI 6–10) or very large effect (DLQI >10) on the patient's QoL. Details of age, sex and immunosuppression regimen were analysed for each group using the Kruskal–Wallis and Fisher exact tests.

The effects of the various skin complications on QoL after transplantation were analysed individually using ordinal logistic regression. Factors with significant results in the univariate analysis were combined with age, sex, duration and type of immunosuppression in a multifactorial model. The reason for this approach was to examine any effect of skin complications in the presence of confounding demographic variables. Significant variables in this model were deemed independent for their association on the QoL outcome.

A probability of 5% was considered to be significant (i.e. $P < 0{\cdot}05$). All of the statistical analysis was conducted using Stata (version 8·0, College Station, TX, U.S.A.).

Results

All 173 RTR, 100 males and 73 females, invited to complete the questionnaire agreed to do so. The study population had a mean age of 48·3 years and a mean duration of 10·4 years since transplant. At the time of the study, 116 of the RTR were receiving immunosuppression based on ciclosporin and 41 were receiving tacrolimus-based immunosuppression. Sixty-five (38%) of the RTR had a total score of 0 while 84% had a total DLQI score of <5 indicating that skin disease related to post-transplant immunosuppression had little impact on the QoL of most RTR (Table 1). Of the remainder, 16% of RTR scored >6 on the DLQI with 4% scoring >10. These patients felt that the condition of their skin, however, was having a very significant impact on their life quality. An increasing DLQI score was significantly associated with female sex ($P = 0{\cdot}041$), younger age ($P = 0{\cdot}008$), and increasing number of post-transplant skin diseases ($P = 0{\cdot}001$). All the patients whose QoL was most affected (DLQI score >10) were

Table 1 Demographic and immunosuppression details as per Dermatology Life Quality Index score

	Group 1 DLQI = 0 n = 65	Group 2 DLQI (1–5) n = 80	Group 3 DLQI (6–10) n = 21	Group 4 DLQI >10 n = 7	P-value
Male (n)	45	44	9	2	0·041
Female (n)	20	36	12	5	
Mean age (SD)	50·7 (13·9)	48·9 (13·2)	41·2 (15·1)	40·1 (9·9)	0·008
Mean duration transplanted, years (SD)	9·6 (6·6)	10·9 (7·6)	11·4 (7·2)	11·9 (6·6)	0·619
Post-transplant skin diseases					
Mean number (range)	1·8 (0–6)	2·4 (0–6)	3·2 (0–10)	4·6 (2–9)	0·001
CyA (n)	45	49	15	7	0·48
FK506 (n)	16	20	5	0	

CyA, ciclosporin-based immunosuppression; FK506, tacrolimus-based immunosuppression.

Table 2 Post-transplant skin manifestations correlated with Dermatology Life Quality Index score

Skin problem	Number	% of patients with DLQI of 0/1–5/6–10/>10	Coefficient	95% Confidence interval	P-value
Dry skin	79	33/51/57/57	0·697	0·125–1·269	0·017
Viral warts	56	29/30/52/29	0·372	−0·234–0·978	0·23
Skin cancer history	51	35/28/19/29	−0·460	−1·082–0·162	0·15
Itch	43	5/35/38/57	1·601	0·913–2·290	< 0·001
Hypertrichosis	36	17/18/33/57	0·744	0·020–1·467	0·044
Surgery scars	33	20/15/24/43	0·183	−0·557–0·923	0·63
Sebaceous gland hyperplasia	30	9/19/29/43	1·049	0·289–1·809	0·007
Acne	28	6/20/29/29	1·138	0·372–1·903	0·004
AV fistula	21	15/8/19/14	−0·177	−1·083–0·728	0·70
Ecchymoses	14	8/8/5/29	0·256	−0·812–1·324	0·64
HSV history	8	2/3/10/43	2·558	1·080–4·035	0·001
Genital warts	3	0/1/5/14	2·568	0·442–4·694	0·018

AV, arteriovenous; HSV, Herpes simplex type 1 infection.

receiving ciclosporin-based immunosuppression. However, the immunosuppressive regimen (P = 0·4) or mean duration on immunosuppression (P = 0·6) did not show significant differences relative to the DLQI score.

The group of RTR with a DLQI score of >10 (very large effect on QoL) had more women (71%) and were younger (mean age 40·1 years) when compared with those with a DLQI score of 0 (31% female, mean age 50·7 years). RTR who scored >10 had a higher mean number of skin diseases (4·6) than the mean for the whole study population (2·4). Analysis of the findings of RTR with a DLQI score of 0 (no effect on QoL) showed a proportion with no reported skin findings or symptoms but also a significant number with some skin disease, which was having no adverse effect on their quality of life. Dry skin (33%), viral warts (29%), history of skin cancer (35%), hypertrichosis (17%) and visible surgery scars (20%) were the most common skin manifestations present on examining this group. Of those with a history of skin cancer, 45% had a DLQI score of 0 and 90% of patients with skin cancer scored <5.

Dry skin (P = 0·017), itch (P = 0·0001), hypertrichosis (P = 0·044), sebaceous gland hyperplasia (P = 0·007) and acne (P = 0·004) all occurred in >15% of the study population and were factors perceived to have a significant impact on the QoL (Table 2). The presence of genital warts (three patients) and a history of at least four cold sores in the past year (eight patients) were much less common but also had an important impact on the QoL measure. The presence of viral warts on the face or extremities, the presence or history of skin cancer, visible surgical scars, a dilated arteriovenous fistula or ecchymoses on the forearms did not significantly affect the DLQI score.

The multifactorial model of QOL outcome (Table 3) reveals age and sex to be significant independent predictors of higher DLQI scores after transplantation. The negative coefficient for age on ordered QoL groups show that younger patients are more likely to experience a poorer quality of life. The positive coefficient for female patients demonstrates a poorer QoL for these patients. Sebaceous gland hyperplasia, itch and acne also retain their significance in this model (P < 0·05).

Table 3 Multi-factorial model of quality of life outcome

	Coefficient	Standard error	95% Confidence interval	P-value
IS regimen[a]	−0·029	0·399	−0·812–0·753	0·94
Age	−0·042	0·013	−0·066–-0·017	0·001
Female sex	1·365	0·363	0·654–2·076	<0·001
Duration on IS	0·041	0·022	−0·002–0·084	0·06
Itch	1·833	0·438	0·974–2·691	<0·001
Acne	0·964	0·427	0·127–1·800	0·024
HSV history	1·364	0·816	−0·236–2·963	0·095
Genital warts	1·085	1·424	−1·706–3·875	0·45
Hypertrichosis	0·551	0·426	−0·284–1·385	0·196
Dry skin	−0·068	0·378	−0·808–0·672	0·857
Sebaceous gland hyperplasia	1·381	0·442	0·515–2·247	0·002

HSV, herpes simplex type 1 infection; IS, immunosuppression; [a]Ciclosporin-based vs. tacrolimus-based immunosuppression

Herpes simplex virus (HSV) infection, genital warts, hypertrichosis and dry skin are all nonsignificant at the 5% level, while the duration of immunosuppression is narrowly nonsignificant in the presence of other confounding variables. Ciclosporin-based immunosuppression when compared with tacrolimus-based immunosuppression did not have a significant impact on the DLQI score in the multifactorial model.

Discussion

This study has illustrated that skin disease related to post-transplant immunosuppression has a minimal impact on the QoL of many RTR but does have a significant impact on 16% of them, especially the young and female RTR, those with multiple skin problems, those with dry itchy skin, hypertrichosis, sebaceous gland hyperplasia, acne, genital warts or recurrent HSV infections.

QoL is a concept which has evolved from the World Health Organization's definition of health as 'a state of complete physical, psychological and social well-being and not merely the absence of disease or infirmity'.[13] While this concept has long been recognized, it is only recently that QoL measures have been introduced as an additional assessment variable in clinical prioritization[14] for many fields including that of renal transplantation.[15] Measures of QoL have particular significance for diseases of the skin because, although not generally life threatening, they can have an important effect on the patient's physical health, psychological status and social relations.[16]

Skin conditions that affect visible sites such as the hands or face cause greater distress than those that are socially invisible. Facial acne, sebaceous gland hyperplasia and hypertrichosis are particularly common in RTR and were all significantly associated with higher DLQI scores. Significance also applied to conditions that are perceived as infective (HSV1 infection, genital warts) and those that cause discomfort (dry skin, itch). Cutaneous manifestations such as bruising, the presence of a fistula, viral warts, surgery scars or a history of skin cancers did not significantly equate with high DLQI scores. Such manifestations may be sufficiently commonplace among the transplant community that they are not perceived as distressing. This study examined the association between a history of skin cancer and the DLQI score and found that it was not significant despite the preponderance of patients with post-transplant nonmelanoma skin cancer (NMSC) on sun-exposed sites. This supports previous studies demonstrating that NMSC of the head and neck has a minimal effect on DLQI with but a slight improvement following treatment.[9] Alternatively, this may reflect limitations of the DLQI to assess the QoL impact of skin cancer.

It is insufficient to quantify the impact of specific skin diseases based on site, distribution and severity without considering the attitude of the individual. Studies that have asked doctors to estimate a patient's QoL have shown that assessment by the doctor may differ significantly from self-assessment by the patient.[17] Certain older patients in this transplant population were not bothered by cosmetically significant sebaceous gland hyperplasia although younger patients by contrast often experienced significant psychological and social distress from comparatively minor skin changes.

This observation is borne out by the continued significance of younger age and female sex in a multivariate analysis of the factors associated with higher DLQI scores. Not surprisingly, women registered a greater QoL handicap than men for most post-transplant skin complications, a fact that mirrors the findings of numerous studies in non-transplanted individuals.[7,10]

QoL after transplantation may influence the patients' immunosuppressive therapy and treatment protocols as well as their motivation to comply with medication regimens. Post-renal transplant noncompliance is currently the third leading cause of renal graft loss; chronic rejection may often result from multiple episodes of non-compliance.[11] This again may be particularly relevant in young and female RTR. The development of newer immunosuppressive agents allows greater scope for tailoring the immunosuppressive regimen to the individual patient risk profile. While initial attempts to differentiate between ciclosporin-based and tacrolimus-based regimens after renal transplantation failed to show any difference in QoL measures[18] a more recent study concludes that tacrolimus has significantly better QoL outcomes than ciclosporin.[19] Although this study did not compare DLQI before and after switching immunosuppressant drugs, a number of patients did report fewer skin complications after switching from ciclosporin. Hypertrichosis and sebaceous gland hyperplasia, complications that in our patient group had a significant impact on DLQI, are not uncommon with long-term ciclosporin use but are less often seen with the newer agents. These cosmetic issues, along with the improved rates of rejection seen with newer agents, have altered the practice of prescribing ciclosporin-based immunosuppression for newly transplanted patients in many centres.

Health service economics are increasingly important in determining how finite resources should be spent. The purpose of a health service is to provide the best care to patients. Up to now decisions on which immunosuppressant drugs are optimal for patients have been based on cumulative clinical experience and on clinical trials determining safety and efficacy, but drug costs and quality of life issues have not been so much to the fore. This study has illustrated the profound effect of post-transplant skin complications on the quality of life in particular for female and younger RTR. It may be helpful to physicians to realize the effect of complications of immunosuppression on these patient groups so that they can adopt strategies and treatments to address these problems with a targeted choice of immunosuppressive regimen, and referral to a dermatologist for appropriate treatment of any skin complication.

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