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REVIEW

Prevalence, consequences, and determinants of nonadherence in adult renal transplant patients: a literature review

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Summary

This literature review summarizes the evidence on the prevalence, determinants, clinical and economic consequences of nonadherence with immunosuppressive drugs in renal transplant patients. A literature search yielded 38 articles measuring nonadherence by self-report, collateral report, assay, refill prescriptions or electronic monitoring. The weighted mean prevalence of self-reported nonadherence was 28%. Nonadherence is associated with poor clinical outcomes, contributing to 20% of late acute rejection episodes and 16% of the graft losses (weighted means). In addition, nonadherence results in lower lifetime costs because of shorter survival, yet also in a lower number of quality adjusted life years. Consistent determinants of nonadherence were younger age, social isolation, and cognitions (e.g. low self-efficacy, certain health beliefs). Determinants concerning the health care system/team seem to be underinvestigated. Because the evidence summarized in this review is based on older immunosuppressive regimens, further research should focus on prevalence, determinants and consequences of nonadherence with newer immunosuppressive regimens.

Introduction

Despite the introduction of powerful immunosuppressive agents and a continuous decrease of acute rejection episodes over the last decades, recent data show that long-term renal allograft survival only marginally improved. Indeed, graft survival in first transplants only increased by a mere 5 months between 1988 and 1995 [1]. In addition, overall graft survival remained at the same level between 1995 and 2000 [2]. This suggests that current therapeutic interventions do not efficiently prevent the development of chronic allograft nephropathy, which accounts for 40–50% of late allograft losses [3]. Chronic allograft nephropathy is the consequence of any immunological (i.e. clinical or subclinical allograft rejection) or nonimmunological injury (e.g. calcineurin-inhibitor nephrotoxicity, hypertension, infections) to the renal allograft. The immunosuppressive therapy, which should be adapted to the needs of every patient, balances the risks for rejection and over-immunosuppression.

Nonadherence with the immunosuppressive therapy is a behavioral factor that also needs to be scrutinized. Although nonadherence is regarded as one of the major causes of late renal allograft failure [4], because of variability in exposure of the kidney to immunosuppressives [5–9], or simply by a discontinuation of drug intake [10,11], it only receives limited attention when discussing the etiology of graft loss in the literature [3,12,13]. Understanding the behavioral dimension of transplant patients' management in view of prevalence, consequences

and determinants of nonadherence with immunosuppressive drugs is a prerequisite for targeting nonadherence as a potential modifiable risk factor for poor outcome. The goal of this literature review is therefore to summarize the existing evidence on nonadherence with the immunosuppressive therapy in adult renal transplant recipients, more specifically to summarize and discuss: (i) measurement methods for assessing nonadherence, (ii) prevalence, (iii) clinical as well as economical consequences, and (iv) determinants of nonadherence.

The behavioral dimension of kidney transplantation

The therapeutic regimen of renal transplant recipients consists of medication taking, infection prevention, smoking cessation, clinic visit attendance, and of following guidelines concerning alcohol intake, diet and exercise. 'Adherence', a key component of the behavioral dimension of transplant patients therapeutic regimen, also called 'compliance' or 'concordance', refers to *the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with the agreed recommendations from a health care provider* [14].

Adherence with the immunosuppressive regimen can be measured by various direct and indirect methods. Direct methods refer to observation and assay of medications or medication by-products. Indirect methods include self-report, pill count, prescription refills, collateral report, clinical outcome, and electronic monitoring (EM). EM refers to a pill bottle that contains a microprocessor fitted cap to save the date and time of each opening [15]. Despite the fact that the registration of a pillbox opening does not prove ingestion, EM shows superior sensitivity compared with other methods, as shown in cross-validation studies [16]. Moreover, EM allows assessing nonadherence as a continuous variable in a multidimensional manner (i.e. the taking and timing dimension of medication taking). Self-report often results in underreporting of nonadherence [16,17]. Assay, despite being a direct method, only allows determining medication intake over a limited time period, depending on the half-life of the drug. Also, 'white coat adherence', referring to patient's correct intake in the light of a pending clinic visit, might further distort interpretation of therapeutic blood levels [18].

We screened abstracts from the database of Medline, Cinahl and Psycinfo (1988–2004) for English, Dutch, French or German studies focusing on prevalence, determinants and consequences of nonadherence with immunosuppressive drugs in nonpediatric renal transplant patients, using the following keywords: (kidney or renal) and transplan* and (adheren* or complian* or nonadheren* or noncomplian*). The Medline search yielded 569 abstracts, of which 34 focused on prevalence and/or consequences and/or determinants of nonadherence. Exploration of the reference lists yielded another four articles. The Cinahl and Psycinfo databases did not provide extra studies.

Prevalence of nonadherence

Seventeen studies reported on prevalence of nonadherence with immunosuppressive drugs in kidney transplantation (Table 1). The prevalences of nonadherence varied widely, ranging from 2 to 67%, depending on the used operational definitions, case finding and measurement methods. A weighted mean prevalence, calculated over all studies that measured nonadherence by self-report, was 27.7% ($n = 10$). One study, the only one measuring nonadherence by medical chart review, found a very low nonadherence prevalence of 2%. Given the higher prevalences in other studies, chart review seems to lack sensitivity in capturing nonadherence [19]. The fact that nonadherence is not assessed as a standard clinical parameter in most transplant programs may explain this low percentage.

Two studies provided electronically monitored period prevalence estimates of nonadherence, using adherence parameters that express the taking and timing dimension of nonadherence [20,21]. Although no clinical meaningful cut-off to classify patients in adherers and nonadherers in the renal transplant population has been developed so far, these studies considered patients as being nonadherent if they had taken <90% of the prescribed doses, resulting in a 26% [21] and 20% [20] nonadherence prevalence. Future studies should define cut-off values, indicating which level of nonadherence results in late acute rejection or graft loss. Research in the heart transplant population already showed that minor deviations from dosing schedule were associated with late acute rejections (>1 year after transplantation) [22].

This evidence about the prevalence of nonadherence with immunosuppressive regimen in renal transplantation indicates the widespread nature of the problem. To better understand the relevance of nonadherence, its relation with poor outcomes (e.g. acute rejection episodes and allograft loss) needs to be explored.

Consequences of nonadherence

Consequences of nonadherence can be categorized in clinical and economic consequences. Clinical consequences can be examined by assessing the effect of subclinical nonadherence on clinical outcomes, or by retrospectively looking for causes of acute rejections or graft losses.

Table 1. Studies estimating the prevalence of nonadherence with immunosuppressive medication in renal transplant recipients.

Study	Description of the sample	*n*	Nonadherence conceptualization and measurement	Results: prevalence of nonadherence
Butler *et al.* [21]	RTX recipients >18 years old, ≥6 months post-transplant; on Pred; UK	60	Electronic monitoring during 6 weeks (i) Missed at least 20% of the prescribed doses (ii) Missed at least 10% of the prescribed doses	 (i) 12% (ii) 26%
Ghods *et al.* [24]	RTX recipients >1 year post-transplant; 95% on CyA (+sometimes MMF), 5% are on AZA/Pred; Iran	267	Self-report: missing ≥3 doses per month	21=7.9%
Vasquez *et al.* [25]	Adult RTX recipients with functioning graft; on CyA and MMF; US	95	(i) Self-report: missed dose since the last visit or in the week prior to receipt of the study survey (ii) Assay: three successive CyA < 50 ng/ml or FK < 5 ng/ml in the absence of CNI metabolism affecting drugs, or absorption problems	(i) 44 = 46.3% (ii) 16 = 16.8% Total: 52 = 55%
Nevins *et al.* [20]	Newly transplanted RTX recipients, transplanted between 1993 and 1995; on AZA; US	134	Electronic monitoring during 6 months after discharge (i) Average percentage of correctly dosed days (ii) Percentage taking less than 90% of the prescribed doses	 (i) 88.1% (ii) 20%
Butkus *et al.* [26]	RTX recipients, RTX between 1992 and 1997; US	128	Not stated	11 = 9%
Chisholm *et al.* [65]	RTX recipients >18 years old, 8–12 months post-transplant, receiving immunosuppressives at no cost, RTX between 1997 and 1998; patients on CNI; US	18	Refill record count: nonadherence if <80% of prescribed medication refilled	12 = 66.7%
Teixeira de Barros *et al.* [56]	RTX recipients transplanted between 1995 and 1997; Portugal	113	Six 4-monthly self-report evaluations in 2 years period: admission ≥2 evaluations to having skipped a dose or to having deviated >2.5 h from the prescribed dosage schedule	18 = 16.8%
Raiz *et al.* [57]	RTX recipients >18 years old, first transplants, with functioning graft >12 months post-transplant; transplanted between 1985 and 1994; US	357	Self-report: not taking medications like instructed less than once a week or more	32.5%
Greenstein & Siegal [58]	RTX recipients >18 years old, with functioning graft; on CNI; 56 centers in the US	1402	Self-report: having missed ≥1 doses of immunosuppressive medication in the previous 4 weeks	314 = 22.4%
Siegal & Greenstein [59]	RTX recipients >18 years old, with functioning graft, on CyA, five centers, US	519	Self-report: having missed ≥1 doses of immunosuppressive medication in the previous 4 weeks	69 = 18%
De Geest *et al.* [31]	RTX recipients >18 years old, at least 1 year post-transplant, Dutch speaking; on CyA; Belgium	148	Self-report	22.3%
Frazier *et al.* [61]	RTX recipients, transplanted between 1987 and 1990; US	241	Self-report: 11 items scale measuring medication nonadherence, defined as missing a dose at least 'sometimes'	45%

Table 1 (contd)

Study	Description of the sample	*n*	Nonadherence conceptualization and measurement	Results: prevalence of nonadherence
Sketris *et al.* [60]	RTX recipients on CyA; sampled from two centers in Canada	361	Self-report: admission of at least one of the criteria: – taking a smaller or larger dose > once per week – taking >2 h before/after the indicated time > once per week – not taking a dose > once per month	65%
Kalil *et al.* [19]	RTX recipients >1 year post-transplant, transplanted between 1976 and 1982; on AZA/Pred; US	202	Medication nonadherence reported in the medical chart	4 = 2%
Butkus *et al.* [34]	1st cadaveric RTX recipients, transplanted between 1985 and 1991; on CyA; US	100	Composite measure: ≥3 consecutive missed clinic visits, immeasurable blood CyA on 2 consecutive visits in the absence of another explanation, or leaving hospital against advice	10 = 10%
Rovelli *et al.* [51]	RTX recipients >3 months post-transplant, experiencing no rejection <3 m; transplanted between 1971 and 1984; US	260	Medical record report of: (i) Appointment nonadherence (ii) Medication nonadherence: admission of patients/family	47 = 18%
	Same inclusion criteria, but transplanted after 1984. Patients also received adherence enhancing education before transplantation	196	Medical record report of: (i) Appointment nonadherence (ii) Medication nonadherence: admission of patients/family	30 = 15%
Didlake *et al.* [49]	RTX recipients, RTX between 1982 and 1986; on CyA; US	185	Self-report: omitting ≥1 dose per month	36 = 19.5%

AZA, azathioprine; CyA, cyclosporine; CNI, calcineurin inhibitor; FK, tacrolimus; MMF, mycophenolate mofetil; Pred, prednison; RTX, renal transplant.

Clinical consequences

Fifteen studies examined the association between subclinical nonadherence and clinical outcome [19,20,23–34]. Three prospective cohort studies [20,23,32], one of which measured nonadherence electronically [20], demonstrated that nonadherence is a risk factor for late acute rejection and late graft loss (Table 2). These studies only took into account acute rejection and graft loss events if occurring after 3 months [20,32] or 1 year post-transplant [23]. Ten retrospective cohort studies, admittedly a weaker design, further confirmed the relationship between (late) acute rejection [24,25,29–31], graft loss/graft survival [19,26,28–30,34], patient survival [31], and graft dysfunction (defined as serum creatinine being ≥5 mg/dl) [24]. Two retrospective studies focusing on the relationship between nonadherence and chronic allograft nephropathy failed to find a direct link [31,35]. However, it is worth noting that acute allograft rejection is the major risk factor for developing chronic allograft nephropathy [36,37]. Given that nonadherence substantially contributes to late acute rejection [37], an indirect link between nonadherence and chronic allograft nephropathy can be suggested.

Eighteen studies estimated the contribution of nonadherence in the etiology of graft losses and acute rejections, attributing up to 64% of the graft failures [27,28,34,38–49] and 80% of the late acute rejections to nonadherence [50,51], depending on case finding and measurement methods. Averaging these percentages by a weighted mean over the publications that met the methodological requirement of having formally assessed nonadherence, resulted in an estimated contribution of nonadherence to graft losses of 16.3% ($n = 8$), and to late acute rejections of 19.9% ($n = 3$; Table 3).

These percentages probably underestimate the contribution of nonadherence in poor clinical outcome, as assessment of nonadherence in clinical practice rarely occurs in a routine and standardized way. Illustrative in this regard are the results of a study in a single heart transplant center that initially reported to the 'United Network for Organ Sharing' database that nonadherence was the etiological factor in 2% of graft losses. Detailed

Table 2. Prospective cohort studies testing the clinical consequences of nonadherence with immunosuppressive medication in renal transplant recipients.

Study	Description of the sample	*n*	Nonadherence conceptualization and measurement	Outcome	Analysis	Results: consequences of nonadherence
Vlaminck *et al.* [23]	RTX recipients that were >18 years, at least 1 year post-transplant, Dutch speaking; Belgium; on CyA	146	Self-reported nonadherence measured at inclusion, defined as having regular dose omissions in the past year	Late acute rejection (biopsy proven)	Cox regression controlling for other influences	Rejection-free time is shorter in nonadherent than in adherent recipients ($P = 0.04$)
				Graft function	Mixed model	A significantly higher increase in serum creatinine in adherent patients after RTX ($P < 0.001$)
Nevins *et al.* [20]	RTX recipients, >90 days after transplantation discharge, independent medication management; 1993–1995; on AZA; US	134	Electronic monitoring	Late acute rejection (clinical diagnosis or biopsy proven)	Kaplan–Meier	Rejection-free survival is longer in adherent patients ($P = 0.006$)
				Graft survival (all deaths counted as graft loss)	Kaplan–Meier	More graft loss in nonadherent patients ($P < 0.002$)
				Patient survival	Death occurred too infrequently to perform tests	
Hilbrands *et al.* [32]	Adult first or second RTX recipients >3 m post-RTX, cadaveric grafts, no psychiatric disease, no alcohol abuse, knowledge of Dutch; Study was part of a trial comparing CyA with AZA + Pred	113	Pill-count: the sum of the monthly assessed, but dichotomized percentage of prescribed medications taken	Late acute rejection (Biopsy proven in 81%)	Mann–Whitney *U*-test	More underconsumption of medication in patients experiencing rejection ($P < 0.01$)

AZA, azathioprine; CyA, cyclosporine; Pred, prednison; RTX, renal transplant.

Table 3. Studies estimating the contribution of nonadherence with immunosuppressive medication on late acute rejection or graft loss.

Author	Description of the sample (all samples consist of patients experiencing graft loss)	*n*	Nonadherence conceptualization and measurement	Outcome	Results: estimated percentage poor outcomes because of nonadherence
Michelon *et al.* [38]	RTX recipients; RTX between 1977 and 1999; on AZA/Pred, AZA/Pred/CyA, MMF/CyA/Pred, Fk/AZA/Pred; Brazil	1027	Patient admitted that nonadherence was the cause of the graft dysfunction	Graft loss	47 of 448 = 10.5%
Matas *et al.* [39]	RTX recipients; RTX in the 1990s, on CyA, AZA/MMF & Pred; US	534	Nonadherence was mentioned in the medical file	Graft loss	11.7%
Michelon *et al.* [41]	RTX recipients; RTX between 1977 and 1991; on AZA/Pred & AZA/Pred/CyA; Brazil	1027	Patient or relative admitted that nonadherence was the cause of the graft loss when coming back on dialysis	Graft loss	48 of 385 = 12.5%
Gaston *et al.* [28]	Kidney and kidney-pancreas transplantation with graft loss because of chronic rejection beyond 6 months; transplanted between 1992 and 1995; on CyA; US	1005	Two of the following criteria: admission of nonadherence by the patient, documented in the medical record failure to keep scheduled appointments in outpatient transplant clinic, undetectable CyA levels on >1 occasion in the absence of physician instruction to withhold CyA	Graft loss	64 of 184 = 34.8%
Garcia *et al.* [42]	RTX recipients, >6 months post-transplant, RTX between 1977 and 1995. Patients received education about importance of adherence after 1991; Brazil	562	When coming back on dialysis, the patient or a 1st degree relative admitted that regular medication intake was not rule	Graft loss	24 of 139 = 17.2%
Reinke *et al.* [50]	RTX recipients with impaired graft function ≥2 year post-transplant; on CyA/pred, AZA/Pred, CyA/AZA, or triple therapy; Germany	432	Assay of CyA and sometimes AZA	Late acute rejection	Four of 157 = 2.5%
Kiley *et al.* [46]	RTX recipients, RTX between 1985 and 1987; on CyA; US	105	Repeated CyA assays <30 ng/ml in the absence of factors likely to affect the CyA levels	Graft loss	Nine of 14 = 64.3%
Butkus *et al.* [34]	First cadaveric kidney transplant recipients; RTX between 1985 and 1991; on CyA; US	100	≥3 consecutive missed clinic visits; immeasurable blood CyA on two consecutive visits (in the absence of another explanation); or leaving hospital against medical advice	Graft loss	10 of 46 = 21.7%
Hong *et al.* [47]	RTX recipients >1 y post-transplant; RTX between 1983 and 1989; on CyA & tapering Pred; US	654	Self-admission or nonadherence, failure to attend two consecutive visits, or CyA level below 25 ng/ml that normalizes after CyA administration in the hospital	Graft loss	15 of 83 = 18.1%
Didlake *et al.* [49]	RTX recipients; RTX between 1982 and 1986; on CyA; US	531	Initial CyA blood levels <25 ng/ml and rose upon in-hospital administration of the prescribed dose	Graft loss	15 of 126 = 11.9%

Rovelli *et al.* [51]	RTX recipients, >3 months post-transplant, experiencing no rejection <3 m; transplanted between 1971 and 1984; US	260	Medical record report of: (i) Appointment nonadherence (ii) Medication nonadherence: admission of patients/family	Late acute rejection	36 of 74 = 48.6%
	Same criteria, but transplanted after 1984. Patients also received adherence enhancing education before transplantation; US	196	Medical record report of: (i) Appointment nonadherence (ii) Medication nonadherence: admission of patients/family	Late acute rejection	Eight of 10 = 80.0%

AZA, azathioprine; CyA, cyclosporine; CNI, calcineurin inhibitor; FK, tacrolimus; MMF, mycophenolate mofetil; Pred, prednison; RTX, renal transplant.

reevaluation revealed that actually 13% of the graft losses were related to nonadherence [52]. Given the contribution of nonadherence to the development of acute rejection and graft loss, it should be worthwhile to integrate a routine and standardized measurement of nonadherence in transplant registries or large outcome studies. Currently, categories such as 'acute rejection' or 'chronic allograft nephropathy' mask nonadherence, resulting in underreporting of nonadherence as an important contributor to poor outcome [28].

Also, as most studies assessing the relationship between nonadherence and outcome include patients on older immunosuppressants (e.g. azathioprine, cyclosporine), priority should be given in future research to assess if the found associations also apply for newer immunosuppressive regimens (e.g. tacrolimus, sirolimus, mycophenolate).

Economic consequences

Economic consequences of nonadherence have rarely been examined according to the best available standards for economic evaluation [53]. One study estimated that the additional hospital cost associated with nonadherence amounts to $900 per patient per year [54]. This figure, however, incompletely reflects the actual costs, as nonadherence not only impacts upon hospital costs but also on other cost categories, such as ambulatory care costs, nursing home care costs, productivity losses and patients' and their family's out-of-pocket expenses.

To grasp the full economic impact of nonadherence, it is necessary to consider both costs and outcomes in a cost-effectiveness or cost-utility analysis. Nonadherence after renal transplantation may have two opposite consequences that make it difficult to determine *a priori* what its consequences will be on the cost-effectiveness of renal transplantation. On the cost side, nonadherence may entail additional costs because of the occurrence and consequent treatment of late acute rejection or graft loss. However, adherent patients may experience more negative side-effects related to immunosuppressive medication intake that also require additional treatment. The balance between the costs of adherence and nonadherence then becomes blurred. On the outcome side, nonadherence – if deliberate – may increase patients' life satisfaction, for instance through the experience of less side-effects and more flexibility in medication intake. This quality of life improvement may (partly) offset the quality of life loss associated with increased morbidity. Again, the net effect is unclear.

Only one cost-utility study has assessed the economic consequences of nonadherence in a renal transplant population. Cleemput *et al.* [55] found that because nonadherent patients have a lower life expectancy, their lifetime

Table 4. Prospective cohort studies testing determinants of nonadherence with immunosuppressive medication in renal transplant patients.

Study	Description of the sample	*n*	Nonadherence conceptualization and measurement	Determinants assessed	Analysis	Results: factors that were related to nonadherence
Butler *et al.* [21]	RTX recipients >18 years, ≥6 months post-transplant, with functioning graft; UK	60	Six week of *electronic monitoring* of Pred. NA is defined as taking <20% of the prescribed doses	*Socio-economic*: age, gender, marital and employment status, education, social class, ethnicity, social support *Therapy related*: number of RTXs and rejections, graft type, time since RTX, HLA match, time on dialysis, donor diabetes or hypertension, duration of past RTXs *Condition related*: disease severity, past medical details, functional health status, depression *Patient-related*: expectation about the RTX, illness perceptions; medication beliefs	Chi-square test and Mann–Whitney *U*-test Stepwise logistic regression	More NA if younger age ($P = 0.01$), living alone ($P = 0.02$), having a living donor graft ($P = 0.01$), having a lower belief in the need for immunosuppressives ($P < 0.01$), scoring lower on the BMQ-benefits subscale ($P < 0.01$), having negative emotions linked to the transplant ($P < 0.05$) More NA in living donor RTX, patients with a low belief in the need for immunosuppression
Vlaminck *et al.* [23]	RTX recipients >18 years old, ≥1 year post-transplant, Dutch speaking; on CyA; Belgium	146	Self-reported NA measured at inclusion, defined as having regular dose omissions in the past 1 year	*Socio-economic*: age, gender *Therapy related*: donor age, time after RTX, serum creatinine 1 year post-transplant, serum creatinine at inclusion, delayed graft function, number of acute rejections in first year post-transplant, number of transplantations, number of HLA mismatches *Patient related*: perceived social support	Unknown	More NA if no perceived social support ($P = 0.028$)
Teixeira de Barros *et al.* [56]	RTX recipients; transplanted between 1995 and 1997; Portugal	113	*A self-reported* dose omission or intake deviation of >2.5 h in greater than or equal to two 4-monthly evaluations over 2 years	*Socio-economic*: race, employment status, place of residence, marital status, … *Therapy related*: symptom experience *Patient related*: knowledge	Unknown	More NA if a higher level of symptom occurrence ($P = 0.00006$) and symptom distress ($P = 0.00029$), if being single ($P = 0.009$)

Rovelli *et al.* [51]	RTX recipients >3 months post-RTX, no rejection <3 months; RTX after 1984; Patients received adherence enhancing education before RTX; US	196	*Composite measure*: (i) Appointment NA (ii) Medication NA: admission of patients/ family	*Socio-economic*: age, gender, ethnic group *Therapy related*: graft type	Unknown	Ethnic group differences ($P = 0.0001$): more NA in Hispanics and blacks

CyA, cyclosporine; NA, nonadherence; Pred, prednison; RTX, renal transplant.

treatment costs are lower (a dead patient is the cheapest patient). Lifetime costs for adherent patients were estimated to be 38 180€ higher than for nonadherent patients. As for the outcomes, nonadherent patients had a worse outcome than adherent patients in terms of both life expectancy and quality adjusted life expectancy. Both outcomes were summarized in a single outcome measure: Quality Adjusted Life Years (QALYs). Adherent patients gained approximately 1.108 QALYs more after renal transplant (RTX) than nonadherent patients [55]. This implies that the incremental cost-effectiveness of adherence relative to nonadherence after RTX was 35€ 021/ QALY.

The incremental cost-effectiveness ratio will ultimately determine the relative cost-effectiveness of adherence-enhancing interventions [55]. For an adherence-enhancing intervention to be cost-effective, it is important that its cost-effectiveness ratio, added to the cost-effectiveness ratio of adherence relative to nonadherence does not exceed the societal willingness to pay for a QALY.

Determinants of nonadherence

Nonadherence can be considered as a phenomenon that emerges from the interplay of numerous influential factors, categorized into five groups: (i) socio-economic factors, (ii) patient related factors, (iii) condition or disease related factors, (iv) therapy or treatment related factors, and (v) health care system and health care team related factors [14]. Determinants from all categories except for health care system and health care team related factors have to a certain extent been studied in kidney transplant patients [19,21,23–25,27,29–31,34,35,51,56–61]. The following section discusses the findings of these studies. Table 4 summarizes the evidence from all performed prospective cohort studies [21,23,56].

Socio-economic factors

Socio-economic variables have been explored most often. Almost every study included the variable age, showing that nonadherence is nearly consistently associated with being younger [21,24,30,35,51,57–61]. Studies failing to confirm this finding mostly lack a significant subsample of adolescents [23,25,31,51]. One could therefore hypothesize that the found linear association between nonadherence and younger age mainly depends on the presence of (nonadherent) adolescents at the lower end of the age spectrum. Without adolescents, nonadherence might remain quite stable over the life course, at least before major cognitive, sensory and functional impairment appear when becoming older. Facing the aging transplant population, increasing attention needs to be given to

potential age related risk factors. Further socio-economic factors related to higher nonadherence with immunosuppressive therapy in renal transplantation are social network variables [21,24,31,56,57,61]. Nonadherence is associated with living alone [21,31], being unmarried [31,56,61], or perceiving low social support [62]. Analyses investigating the factor education remain inconclusive [19,21,24,25,31,35,57,58,60,61], as some studies did not find any relation with nonadherence [19,21,25,31,35,57], while others found a positive [24,62], or a negative one [58,60,61]. Likewise, socio-economic class [21,24,61] and gender [21,23–25,31,35,51,57,58,60,61] were not consistently related to nonadherence.

In general, it can be stated that socio-economic factors alone, except for younger age and social isolation, show a limited association with nonadherence, in line with evidence from other chronic patient populations [14].

Patient related factors

Patient related factors refer to the resources, knowledge, attitudes, beliefs perceptions and expectancies of the patient [14]. Patient related factors found to be associated with nonadherence with immunosuppressive therapy in renal transplantation are: low self-efficacy with medication intake [31], high levels of anxiety and hostility [60], and an external locus of control [57,60]. External locus of control refers to patient's perception that the evolution of the disease is particularly a matter of chance. Furthermore, health beliefs about the illness or the medication regimen such as believing that the immunosuppressive drugs are not needed to keep the kidney, or that intake of drugs may be delayed, have been found to be related to nonadherence [21,58]. Knowledge about the regimen was positively related to nonadherence in two [25,31] of three studies [25,31,56]. One study investigated the predictive value of pretransplant nonadherence on post-transplant nonadherence, finding also a significant positive relationship [30], in line with the evidence showing that past behavior very well predicts future behavior.

Although a lot of studies investigated patient related correlates of nonadherence in renal transplant, few findings were mutually corroborated. Aside from replicating results, future research could focus on exploring new possible determinants, such as busyness and routine in someone's life style, or engaging in health behaviors (e.g. vaccination).

Condition or disease related factors

The condition or disease related variables depression [61] and dependency on nicotine [24] or on illegal drugs [19,24] showed a positive relationship with nonadherence, whereas having diabetes was related to less medication nonadherence [58], perhaps because of the long-time adoption of adequate health behavior.

Therapy or treatment related factors

Therapy or treatment related factors such as time on dialysis, or being retransplanted were not associated with nonadherence [23,25,29,58,61]. Three studies [59–61] of 8 [23,25,31,57–60] found more nonadherence in patients with a longer post-transplant status, confirming the evidence that duration of the regimen is negatively associated with nonadherence. Other treatment related factors were the number of medications, a factor referring to the complexity of the medication regimen [25], and patients' subjective experiences of the symptoms related to side-effects of medication (e.g. excessive hair growth, moon face) [58,60,63]. Two studies [21,58] of six [21,24,35,51,58,60] detected more nonadherence in recipients of a living donor graft, compared with cadaveric grafts. Future research could focus on the effect of the use of medication reminders (e.g. a pill organizer), changes in the medication regimen, pre-emptive transplantation, or the number of medication intakes per day on nonadherence.

Health care system and health care team related factors

The last category of determinants of nonadherence, health care system and health care team related factors, has been studied far less, indicating a bias in the literature. Two studies investigated the effect of the insurance status on nonadherence [34,58], one of which found more nonadherence in blacks who were not privately insured [34]. Another study tested and detected self-reported differences between European and US renal transplant patients [64]. The lack of evidence about health care system and health care team related factors shows that the patient is implicitly seen as defaulter. As a consequence, opportunities for improving adherence through optimizing the health care system or training the health care worker remain hidden [14,64]. Future research should therefore focus on issues such as the communication style, knowledge, and skills of the health care worker, on time constraints during clinical consultations, and on organization of the follow-up care.

Some general remarks should be made about the studies examining determinants of nonadherence with immunosuppressive medication in renal transplant patients, more specifically about the used data analysis methods. Unlike the studies investigating the clinical consequences of nonadherence, determinant studies often do not mention the used statistical test. If they do, few report on the

distributional properties of the adopted nonadherence operationalization. This lack of statistical background information for model validation jeopardizes the credibility of the presented results, because tests are performed requiring normally distributed data; yet, nonadherence measurements are in many cases highly skewed. Another statistical issue concerns the fact that many studies only report statistical significant findings, although a large amount of not mentioned candidate determinants have been tested. Even if studies report all the results, no study controlled for multiple testing. As a consequence, a significant proportion of the reported statistically significant findings were happening accidentally.

Recommendations for future research

This literature review provides the basis for recommendations for future research:

1 Few studies in this literature review use the sensitive method of EM for measuring nonadherence with the immunosuppressive regimen. Future studies assessing prevalence, determinants and consequences of nonadherence should use EM as a prime measurement method, preferably combined with self-report, assay or collateral report. This triangulation of methods should provide a good basis for a reliable measurement. In addition, studies should state the adopted measurement method and accompanying operational definition of nonadherence.

2 The statistical analysis methods could be enhanced in many studies. The applied statistical tests should be specified, and should not violate underlying assumptions, as is often the case now. Moreover, too many studies have considerable multiple testing problems, not only because *P*-values are not adapted, but also because many studies only report their significant results, and hence, do not mention all variables tested.

3 In view of the exploration of determinants of nonadherence, research should expand to also assessing health care team and health care system related factors, as studies so far have been disproportionally focusing on primarily patient, socio-economic and treatment related factors. Moreover, the use of qualitative research or statistical techniques modeling the interplay of different variables (e.g. path analytic methods) could further enhance the understanding of the different factors influencing nonadherence.

4 Transplant registries and large outcome studies should include nonadherence as a relevant parameter to further assess the impact of nonadherence on outcome on a population basis. To examine the clinical consequences of nonadherence, prospective cohort studies need to be set up that test the effect of nonadherence under the newer immunosuppressive regimens. Sound economical evaluations exploring the economic consequences of nonadherence are needed, as the evidence base in this regard is limited to one study. These studies should take into account both costs and outcomes to allow cost-effectiveness or cost-utility analyses.

5 This review did not include intervention studies, because of the fact that this research area still has to be developed. Intervention programs that target modifiable determinants of nonadherence, embedded in a chronic disease management program, should be tested in with randomized controlled methodology.

Conclusion

Nonadherence with the immunosuppressive regimen in renal transplantation is a common phenomenon with serious consequences. A deeper understanding of the dynamics underlying nonadherence could be achieved by further exploring its determinants. Emphasis should thereby be put on system factors, as these may offer still unknown possibilities to support patients in reaching a higher adherence level.

Conflict of interest

None.

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