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REVIEW ARTICLE

Factors relevant to medication non-adherence in kidney transplant: a systematic review

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Abstract *Background* Medication non-adherence is a major issue after transplant that can lead to misdiagnosis, rejection, poor health affecting quality of life, graft loss or death. Several estimations of adherence and related factors have previously been described but conclusions leave doubt as to the most accurate assessment method. *Aim of the review* To identify the factors most relevant to medication non-adherence in kidney transplant in current clinical practice. *Method* This systematic review is registered in the PROSPERO data base and follows the Prisma checklist. Articles in English in three databases from January 2009 to December 2014 were analysed. A synthesis was made to target adherence assessment methods, their prevalence and significance. *Results* Thirty-seven studies were analysed rates of non-adherence fluctuating from 1.6 to 96%. Assessment methods varied from one study to another, although self-reports were mainly used. It appears that youth (≤50 years old), male, low social support, unemployment, low education, ≥3 months post graft, living donor, ≥6 comorbidities, ≥5 drugs/d, ≥2 intakes/d, negative beliefs, negative behavior, depression and anxiety were the factors significantly related to non-adherence. *Conclusion* As there are no established guidelines, consideration should be given to more than one approach to identify medication non-adherence although self-reports should remain the cornerstone of adherence assessment.

Keywords Graft rejection · Immunology · Immunosuppressive agents · Kidney transplant · Medication adherence · Medication compliance · Prevention and control

Impact of our findings

- It is important to always monitor non-adherence in kidney transplant patients, because it occurs more frequently than thought.
- Non-adherence is likely to be especially prevalent in younger, unemployed kidney transplant patients with low social support and only lower education.

Introduction

Non-adherence to the immunosuppressive regimen is a major issue after solid organ transplant possibly leading to misdiagnosis, rejection, poor health affecting quality of life, graft loss or death [1–16]. Its prevalence ranges from 20% to 50% [17]. The Drug Trend Report identified in 2014 a mean non-adherence rate of 33% [18]. Non-adherent individuals have a threefold higher risk of late acute rejection episodes and a sevenfold higher risk of graft failure [19, 20]. The negative impact of non-adherence has been widely documented through cohorts of transplant patients and is associated with acute (estimated risk from 15 to 60%) and chronic (estimated risk from 5 to 36%) rejection and graft loss

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(estimated risk at 15%) [2, 4, 7, 9, 11, 12, 21]. The mean rejection rate is usually estimated at 35% in kidney recipients [1–3, 7, 8, 11, 16, 20–22].

Studies use different terminology to define adherence: (1) compliance: "the extent to which the patient's behavior matches the prescriber's recommendations"; (2) adherence: "the extent to which the patient's behavior matches the agreed-upon prescriber's recommendations" [16, 23, 24]. These terms are often used interchangeably although their interpretation with regard to patient-healthcare-provider relationship is different. The term "adherence" is now preferred, suggesting that treatment is based on a therapeutic alliance or contract established between patient and physician, with the patient playing an active role [16, 23–25].

Risk factors for non-adherence can be divided into 5 categories: socioeconomic, patient-related, disease-related, treatment-related, and healthcare setting- and provider-related [9, 16, 23, 26]. Previous studies showed that greater adherence was significantly associated with older age, female sex, white race, deceased donors, and tacrolimus immunosuppression [20, 27]. Adherence can be evaluated directly through clinical observations or drug monitoring as well as indirectly through patient interviews, tablet counting, repeat prescriptions, self-reports or electronic monitoring [11, 16, 26, 28]. Electronic monitoring, quoting intake times and amounts, is the gold standard; however, it cannot verify that pills have indeed been ingested [8, 11, 16, 26, 28, 29]. Direct methods also have limitations. They reflect a given time and not necessarily an overall period. In fact, just before a medical appointment there may be an improvement, known as "white-coat adherence" [15, 16, 26]. To date, no faultless adherence assessment exists; only a multiple approach can offer a high level of sensitivity and specificity [16, 26]. Adherence is a dynamic process and whatever the measures used, they must be repetitive over time to be accurate [16].

Aim of the review

The first objective is to highlight factors most relevant to medication non-adherence, specially with regard to immunosuppressive drugs or the overall medication regimen. The second objective is to discuss the available questionnaires and their reliability for use in kidney transplant patients.

Method

Search strategy and study selection

The present review has been registered in "PROSPERO International prospective register of systematic reviews" under ID CRD42015007393 and respects the Prisma criteria. In May and June 2015, literature was systematically searched through computerized Medline, Web of science, and the Cochrane library. The search was limited to the last 5 years (January 2009 to December 2014) to take current practice into account. The following Mesh key terms "Adherence", "compliance", "medication adherence", "medication compliance", "treatment refusal", "patient compliance", "kidney transplant" were combined.

The review included primary research studies on factors related to adherence or non-adherence in adult kidney recipients at any time after transplant, regardless of study duration or design. Our search was restricted to original English-language studies on subjects aged 18.

Data extraction and quality assessment

The first data extractions on titles and abstracts only were made by reader SB, then reviewed by two other readers (BD, MH). Reader SB completed a full-text study of the relevant papers. The following data were collected using a structured data collection sheet: year of publication, aim, study design, patient demographics and medication adherence results.

To critically assess the quality of these studies, the CONSORT checklist for randomized controlled trials, the Newcastle–Ottawa Scale for non-randomized studies and the Blaxter criteria for qualitative studies were used [30–32]. For comparison, the quality score was converted to a percentage.

Statistical issues

A meta-analysis was not advisable due to heterogeneity in interventions, methods and reported outcomes. Some papers reported no statistical analysis, others univariate associations, multivariate associations and some both. We report only factors significantly relevant to non-adherence.

Results

Study characteristics

A total of 37 studies were included and selection steps are reported in Fig. 1.

Only 2 (5%) were randomized, 35 (95%) were observational, mainly prospective (94%). Cohort sizes ranged from 15 to 32,757 patients; 3 studies included 15,525, 31,913 and 32,757 patients respectively [8, 27, 33]. Mean age was 51.1 ± 6.1 with a greater proportion of men (mean 59%). Adherence was measured at different times after

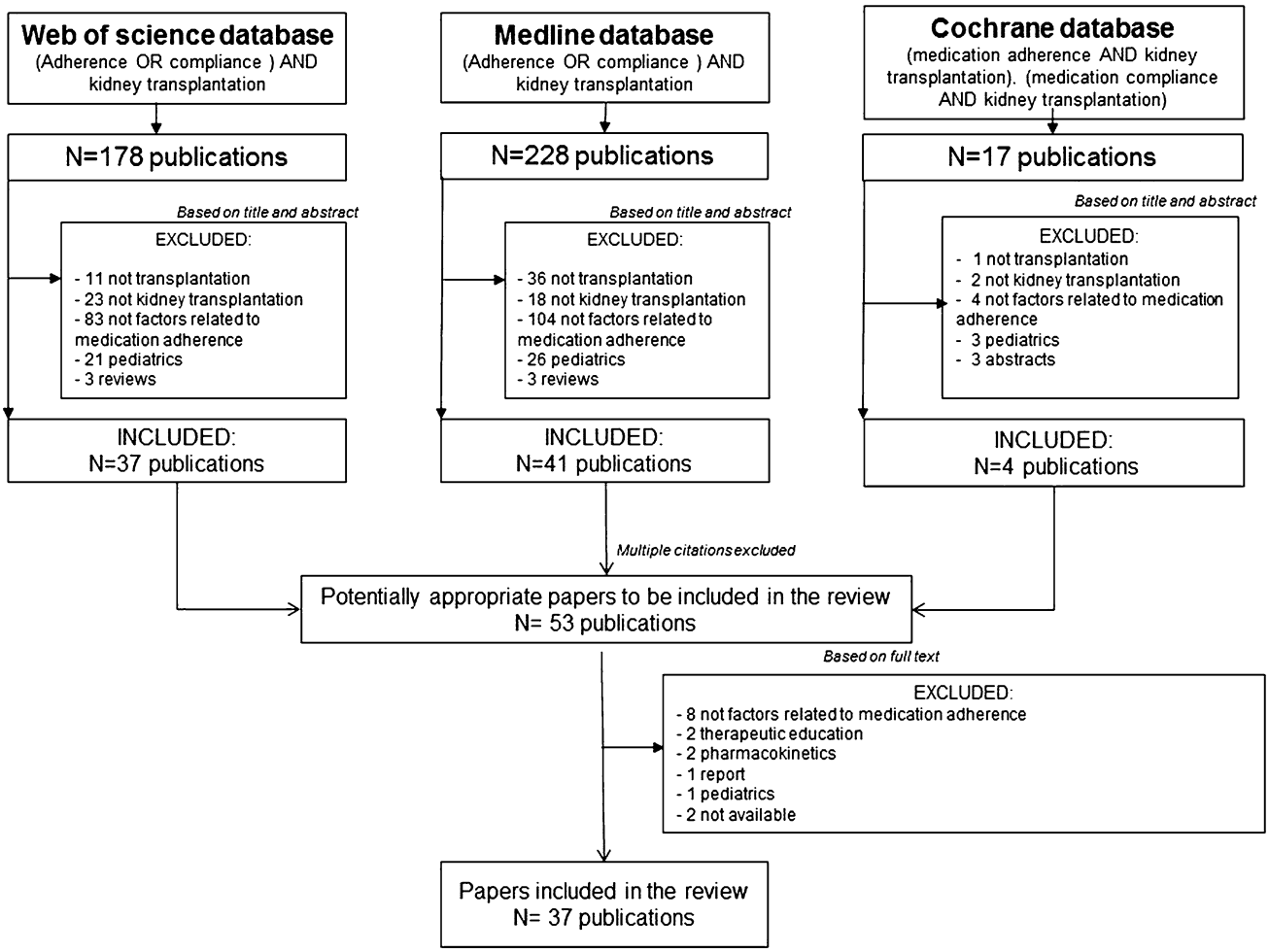

Fig. 1 Literature search. Specific search combinations used in each database: (1) Medline via Pubmed "[(Adherence OR compliance OR medication adherence OR treatment refusal OR patient compliance) AND kidney transplant]"; limits: from 2009 to 2014, age ≥18 years old, English-language. (2) Web of science "[(Adherence OR compliance OR medication adherence OR treatment refusal OR patient compliance) AND kidney transplant]"; limits: from 01/01/2009 to 31/12/2014. (3) Cochrane library "(medication adherence AND kidney transplant), (medication compliance AND kidney transplant)"; limits: from 01/01/2009 to 31/12/2014

transplant, from baseline to more than 25 years after, but mainly at 46 months (about 4 years) after transplant.

Measurement methods

Adherence was assessed through: electronic monitoring, immunosuppressant blood levels, patient interviews, self-reports, refills, pill counts, physician or nurse discernment, in 9 (24%), 5 (11%), 3 (8%), 23 (62%), 4 (11%), 1 (3%) and 2 (5%) studies, respectively. In 6 studies authors measured adherence through an association of methods, mainly self-reports, blood assays, electronic monitoring and/or practitioners' reports [9, 15, 34–37]. 5 studies considered CNI trough blood levels as markers of non-adherence [9, 15, 34, 35, 37]. No studies considered the blood level variation of CNI or any other immunosuppressant as a model to detect non-adherence (Table 1).

Twenty-seven different self-reports (summarized in Table 2) assessed distinct aspects related to adherence: 6 (22.2%) drug-related factors (medication adherence), 12 (44.4%) patient-related factors (beliefs, satisfaction, behavior), 3 (11.1%) psychological disorders (depression, anxiety), 2 (7.4%) quality of life, and 4 (14.8%) social support. The Basel Assessment of Adherence Scale to Immunosuppressive drugs (BAASIS), the Beck Depression Inventory scale (BDI), and the Immunosuppressant Therapy Adherence Scale (ITAS) were the 3 questionnaires used in these studies.

The prevalence of non-adherence depended on the measurement method, and ranged from 1.6 to 58.7%. It was not computable in 3 studies [3, 38, 39].

An average quality score of 48% (Table 1, right column) was obtained, ranging from 22 to 92%. The low quality score was mainly due to the small size of cohorts in

Table 1 Characteristics of included studies

SSource	Study design	Sample size	Mean age (years)	Men (%)	Mean time since Tx (months)	Method of assessment	NA rates (%)	Factors significantly related to NA	Quality ratings (%)
Eisenberger et al. [40]	Prospective observational study	20	51.7	75	6	Electronic monitoring	Taking NA: overall 0.6%, Timing NA: overall 15.5%	NS	56
Israni et al. [29]	Prospective observational study	243	47.7	63	28.8	Electronic monitoring	At 6 months: 68%, 20%, 12% patients had a rate of NA < 15%, 15 < NA < 50% and >50%, respectively	NS	44
Kuypers et al. [56]	Prospective randomized multicenter controlled trial	219	Adults	59	36	Electronic monitoring	About 25% NA rate for patients with once daily tacrolimus formulation, and 40% for patients with twice daily formulation	Number of intakes per day, evening dose	92
Nevins et al. [52]	Prospective observational study	195	48	57	First year of transplant	Electronic monitoring	22.6% patients demonstrated A decline of 7% or more in month 2 versus month 1. 77.4% had either stable or improving rates of A during their second month after Tx	Complexity of treatment, number of doses per day, time after transplant (>6 months)	44
Russel et al. [10]	Prospective randomized, controlled pilot trial	15	51.5	47	ND	Electronic monitoring	50%	Forgetfulness	76
Russell et al. [48]	Prospective descriptive, correlational, longitudinal design	121	>21	63	56.4	Electronic monitoring	61% of the participants below the medication A score of 0.90 over the 11-month monitoring period and 41% below 0.80	Self efficacy, older age	56
Russel et al. [28]	Prospective descriptive study	73	61.37	58	ND	Electronic monitoring	The mean medication A score for those who considered MEMS had a negative/neutral effect on their medication taking was 0.76 (max 1) whereas the mean medication A score for those who considered MEMS had a positive effect on their medication taking was 0.70	Forgetfulness	56
Brahm et al. [2]	Restrospective cross-sectional study	288	48.6	61.5	89	Refill	58.7%	Young age (39–46 years old), fully employed, tacrolimus, worse eGFR (45.3 ± 21.6 ml/min)	67
Pinsky et al. [8]	Retrospective cohort study	15.525	Between 24 and 44	59.7	3.6	Refill	At 1 year: poor A, fair A, good A, excellent A were 24.8%, 24.7%, 26.5%, 24% respectively. At 3 years low A, normal A,and highAwere 23.1%, 70.6% and 6.3% respectively	Female gender, younger age (0–24 years old), 0–24 months dialysis duration, CNI with either azathioprine or rapamycin, graft failure and death	67
Spivey et al. [27]	Retrospective observational study	31.913	48	58.6	45.6	Refill	Mean MPR for the sample was 0.56 with a median of 0.58 (risk of graft failure when <0.8)	Non-white, males, older age, taking cyclosporine, and living donor transplants	56
Burkhalter et al. [42]	Prospective cross-sectional design	926	59.7	63	113	Self report	35%	Younger age, male, long time since Tx, depression and anxiety	22
Cheng et al. [53]	Prospective cross-sectional survey	412	51.5	53	97	Self report	21.4%	Memory impairment, medication side effects	44
Chisholm-Burns et al. [47]	Prospective cross-sectionnal survey	512	52.37	61.3	109	Self report	34.5%	Forgetfullness, low satisfaction, patient behaviors, older pzatients	56

Table 1 continued

SSource	Study design	Sample size	Mean age (years)	Men (%)	Mean time since Tx (months)	Method of assessment	NA rates (%)	Factors significantly related to NA	Quality ratings (%)
Chisholm-Burns et al. [3]	Prospective cross-sectional survey	61	48.85	47.8	87	Self report	Nearly perfect IS medication A	Low social support, forgetfullness	33
Constantiner et al. [38]	Prospective observational study	94	44.1	60	42	Self report	Nearly perfect IS medication A	Too many dosages per day, too many pills per dose, having to remember to take their medication, perceived side effects, skipping a dose to feel better, failing out of medication, depression	33
Couzi et al. [9]	Prospective, noninterventional cohort study	312	49.5	68.3	First 2 years post Tx	Self report	36%	Forgetting to take their medication or taking it at the wrong time, young age, single, small number of tablets, adverse events, longer time since Tx	33
Cukor et al. [57]	Prospective observational study	94	44.1	60	42	Self report	34%	Depression	33
Goldfarb-Rumyantzev et al. [11]	Prospective observational study	199	43	67	57.5	Self report	Taking NA 21%, timing NA 33%	Younger age, greater comorbidity, living donor and full-time employment	33
Jindal et al. [33]	Retrospective cohort study	32.757	46.75	60.6	24	Self report	6.7%	Younger age (43.3 ± 14.1 years old), male gender, 12 or less years of education, depression, long time since Tx, diabetes, hypertension, ischemic heart failure, tobacco, peripheral vascular disease, less HLA missmatch, black race, living donor	56
Lalic et al. [55]	Prospective observational study	60	44.45	63.3%	5.34	Self report	28.3%	Forgetfullness, low tacrolimus blood levels	44
Lin et al. [49]	Prospective cross sectional study	101	46.6	48.5	31.2	Self report	Very low (mean score 4.8/5)	Unmarried status, not enough financial status, time after Tx	33
Massey et al. [46]	Prospective observational study	113	53	64.6	6	Self report	Six weeks After transplant 17% were nonadherent. Six months after transplant, this increased to 27%	Time after Tx (>6 months), younger age at 6 month post Tx (44.32 +/13.33 years old), retransplant, perception, beliefs, behaviors	33
Obiet al. [23]	Prospective cross-sectional, anonymous, and voluntary survey	312	45	58	>36	Self report	Poor adherent patients 9.9%, and very poor adherent 16, 51%	Complexity of regimen, male gender, young age (teens or 20 s) student status, long time since Tx more than one dose per day	22
Sabbatini et al. [50]	Prospective, observational, open-labeled, nonrandomized study	310	49.3	39.1	7.9	Self report	23.5	Less quality of life, forgetfullness, careless with medication, less social support, difficulties with medical staff, less positive behaviors, previous rejection episode, low anxiety, GFR >60 ml/min, number of intakes per day	56
Shabany et al. [44]	Prospective, descriptive-correlational design	230	41.69	55.2	60	Self report	57.8	Forgetfullness, low quality of life, young age (31–40 years old), >2 years after Tx, after a second Tx	33

Table 1 continued

SSource	Study design	Sample size	Mean age (years)	Men (%)	Mean time since Tx (months)	Method of assessment	NA rates (%)	Factors significantly related to NA	Quality ratings (%)
Tielen et al. [1]	Prospective observational study	26	73	81	5	Self report	30.8% patients had not taken their medication, once or more, over the last month	Unintentional forgetfullness	56
Tsapepas et al. [54]	Prospective, observational study	808	51.7	64	3–24 months	Self report	49.8	More than 3 months after Tx	33
Van Boekel et al. [45]	Prospective cohort study	75	49.6	61.3	3.1	Self report	20.3	Low satisfaction, complicated regimen, age, presence of prednisone, unemployed	33
Weng et al. [51]	Prospective single-center, cross-sectional study	252	54.7	59.9	2.9	Self report	14.3	Low eGFR, missing doses, run out of medication, forgetfullness, depression, stress, lack of employment	33
Gaynor et al. [41]	Prospective observational study	628	48.9	69.4	Baseline to 96 months	Interview	6%	Graft failure, younger age (<50 years old), donor age ≥50 years old, history of coronary artery disease, DGF, and number of DR mismatches	56
Gordon et al. [6]	Prospective observational study	82	47.3	53.7	1.58	Interview	12%	Personal barriers, characteristics of medicines; medication dosage and scheduling and access to medicines and pharmacies	33
Ruppar et al. [39]	Qualitative design	19	52.8	37	300 or longer	Interview	Not computable	Forgetfullness	80
Denhaerynck et al. [35]	Prospective observational study	356	52.9	58.2	70	Self-reporting, electronic monitoring, collateral reporting and blood assay	1.6%	NS	67
Gelb et al. [34]	Prospective observational study	103	50.07	52	96	Self-report, refill, blood levels	Self-report score A: 20.8, refill: 5.8%, blood levels: 15.5%	Long time since Tx, younger age, poor wealth and quality of ideas, depressiv syndroms, low cognitive speed	56
Griva et al. [15]	Prospective cross-sectional study	218	49.67	59.6	5.78	Self report, blood levels	Self-report: 51.4%patients were less than A, blood levels: 25.4%	Number of prescribed medications/dose/scheduling, low belief in necessity of medication, depression, anxiety, patients beliefs, younger age, male gender, lower education, employment, cohabiting/marital relationship, living related donor, low end stage renal disease severity index, greater transplant vintage, cyclosporine	56
Joost et al. [36]	Prospective sequential control group design	67	53	69	6–12 months	Self-report, pill count and electronic monitoring	Self-report: at baseline 3%, at 6 months 0%, at 12 months about 2% of non-adherent. Pill count: mean NA 6.5%. NEMS mean NA 5.5%	Time since Tx	67
Ortega et al. [37]	Prospective cross-sectional multicenter study	206	53.35	61.2	11.57	Blood levels, physician judgment	Blood levels: 31.1% and physician judgment: 29.1%	Less satisfaction, forgetfullness, number of drugs per day, drug regimen	44

NA Non-adherence, *A* adherence, *TX* transplant

Table 2 Self-reports for the assessment of adherence or related factors

	Questionnaires	Factors assessed
Drug related factors	Morisky scale, Basel Assessment of Adherence with Immunosuppressive Medication Scales (BAASIS), Immunosuppressant Therapy Adherence Scale (ITAS), Modified Transplant Symptom Occurrence and Symptom Distress (MTSOSD) scale, Simplified Medication Adherence Questionnaire (SMAQ), Medication Adherence Report Scale (MARS)	Medication A to IS and non IS regimen
Patient related factors	Immunosuppressive Therapy Barriers Scale (ITBS), Beliefs about Medicines Questionnaire (BMQ), Life Satisfaction Index (LSI), The Swiss Transplant Cohort Study Daytime Sleepiness Single-item Scale (STCS-DS, ESS), The Short Test of Functional Health Literacy in Adults (sTOFHLA), Long Term Medication Behaviour Self-efficacy Scale (LTMBS), Life Satisfaction Index (LSI), Multidimensional Health Loc Scales (MHLOC), Transplant Effects Questionnaire, Siegal Scale, Treatment Satisfaction Questionnaire for Medication (TSQM)	Patient satisfactions, beliefs, behaviors
Psychological disorders	Beck Depression Inventory (BDI), Hospital Anxiety and Depression (HAD), Perceived Stress Scale-4 (PSS-4)	Depression, anxiety, psychological distress
Quality of life	Short form 36 (SF-36), Quality of life in renal transplant questionnaire	Health related quality of life
Social support	Interpersonal Support and Evaluation List-12 (ISEL 12), the Social Support Appraisal Index (SSAI), the Transplant Care Index (TCI), Modified Social Support Survey (MSSS-5)	Family, friend, social network support

most studies, the inclusion of volunteers and the absence of control groups.

Factors related to non-adherence

Factors were not computable in only 3 studies (N = 619 patients) [29, 35, 40] (Table 2). Indeed, the authors used a questionnaire to measure adherence and considered a patient as non-adherent if he was below or above the score, but the overall rate of non-adherence in the cohort was not specified.

Socio-demographic status

Age

Young recipients (under 50) were considered as more non-adherent in 13 studies (N = 51,684 patients) [2, 8, 9, 11, 15, 33, 34, 41–46]. In only 8 (N = 34,508) was the age given, mean age being 45 [2, 8, 33, 41, 43–46]. However, in 3 studies (N = 32,546 patients) older recipients, from 50 to 65 or over, were targeted as non-adherent [27, 47, 48].

In 1 study (N = 101 patients) the age factor was significantly related to non-adherence but without further precisions [49].

In the remaining 20 studies (N = 3597 patients), the age factor was neither significant nor assessed but the number of patients was limited (less than 10%).

Gender

Five studies (N = 66,126 patients) related the male gender to non-adherence [15, 27, 33, 42, 43] whereas in 1 study (N = 15,525 patients) females were less adherent [8].

In the remaining 31 studies (N = 6294 patients), it was neither significant nor assessed but again the number of patients was limited (less than 10%).

Social support

Three studies (N = 472 patients) noted a positive association between greater social support (family, friends, emotional support, social network) and adherence [3, 49, 50]. According to Chisholm et al., affectionate support, assistance with daily household functions and forgetfulness were significantly ($p < 0.05$) related to medication adherence [3]. Couzy et al. (N = 302 patients) confirmed this, adding that single patients were significantly more at risk of non-adherence [9]. Conversely, 1 study (N = 218 patients) reported higher rates of non-adherence among those married or co-habiting [15].

For the remaining 32 studies (N = 86,955 patients), this factor was either not significant (9 studies, N = 1311 patients) [1, 2, 10, 11, 36, 44, 46, 48, 51] or not assessed (23 studies, N = 85,644 patients).

Employment and education

Full employment was associated with non-adherence (medication forgotten or taken late) in 3 studies (N = 705 patients) [2, 11, 15]. In 1 study (N = 312 patients) being at home full-time or unemployed was associated with greater adherence [43], whereas in 2 studies (N = 327 patients) it was the contrary [45, 51]. Patients with lower education (12 years and less, according to Jindal et al.) were less adherent in 2 studies (N = 32,975 patients) [15, 33], whereas Lin et al. (N = 101 patients) observed that such patients were better monitored and managed [49].

For the remaining 29 studies (N = 53,743 patients), these factors were either not significant (in 10 studies, N = 2359 patients) or not assessed (in 19 studies).

Disease-related factors

Time elapsed since transplant

If time after transplant was a factor related to non-adherence in 11 studies (N = 35,334 patients), little is known about how long it actually takes to become non-adherent [9, 15, 33, 34, 36, 42–44, 46, 49, 52]. In 3 studies (N = 620 patients) patients became less adherent 6 months after transplant [9, 46, 52].

2 studies, by Burkhalter [42] et al. and Jindal et al. [33]. (N = 33 683 patients) questioned adherence over time, concluding that every five years after transplant, forgetful or timing non-adherence increased by 20%, and overall non-adherence by 16% [42].

For the remaining 26 studies (N = 52,611 patients), the factor "time since transplant" was not significant in 8 studies (N = 1722 patients) and not measured in 18.

Number of transplants

Only 2 studies (N = 283 patients) noted the impact of several transplants [44, 46]. Non-adherence rates were significantly greater after a second transplant.

Type of donor

In 13 studies donors were mainly deceased (N = 67,307 patients) [3, 6, 10, 11, 27, 29, 33, 34, 36, 39, 41, 53, 54] and in 9 living (N = 1274 patients) [1, 15, 39, 43, 44, 46, 49, 52, 55]. In the remaining 16 studies, it was not specified. 5 studies (N = 65,715 patients) reported a relationship between donors and non-adherence [11, 15, 27, 33, 41]. In 4 studies (N = 65,087 patients), recipients from a living donor were less adherent [11, 15, 27, 33].

Drug-related factors

In 23 studies (N = 51,577 patients) authors described co-morbidities (more than 6), number of drugs/day (more than 5), number of pills/day (more than 10), number of intakes/day (more than 2), immunosuppressive drugs (mainly cyclosporine and corticosteroids), low blood levels and side effects as significant risk factors for non-adherence [1, 2, 6, 8–11, 15, 27, 34, 37–39, 43–45, 47, 50–53, 55, 56]. Forgetfulness rather than intention was the main explanation.

In the remaining 14 studies (N = 36,368 patients), drug-related factors were not assessed.

Patient-related factors: beliefs, behavior and satisfaction

Negative beliefs and behaviors, such as low satisfaction have been reported as non-adherence factors in 11 studies (N = 1858 patients) [1, 6, 15, 37, 38, 45–50]. Chisholm et al. (N = 512 patients) observed that non-adherent recipients were more forgetful than adherent recipients, missed more doses of immunosuppressant medications when diverted from daily routines; skipped more doses when short of money, believed immunosuppressant medications disrupted their lives and were not necessary [47].

In the remaining 26 studies (N = 86,538 patients), patient-related factors were not measured.

Psychological illnesses

Depression and anxiety emerged as significant predictors of medication non-adherence (7 studies, N = 34,444 patients) [15, 33, 34, 38, 42, 51, 57]. Individuals with high levels of self-reported depression were significantly less adherent (mainly intentionally) than people with mild depression [15, 57].

In the remaining 30 studies (N = 53,501 patients), psychological illness was not a significant factor in 2 studies (N = 379 patients) and not measured in 28 studies.

Discussion

Strategies are required to improve adherence but can only be effective if barriers are understood. Several of these are:

1. Socio-demographical: youth (≤ 50 years old), male gender, low social support, unemployment, poor education.
2. Disease-related: ≥3 months after transplant, living donor, more than 1 transplant, ≥6 co morbidities.
3. Drug-related: ≥5 drugs/day, ≥2 intakes/day, cyclosporine.
4. Patient-related: negative beliefs, negative behavior and negative satisfaction.
5. Psychological: depression and anxiety.

Socio-demographical factors concord with previous studies [4, 58]. Men often fail to attend control visits, neglect to follow dietary recommendations or stop alcohol intake or smoking. Women support their partners by paying attention to medication intake [15, 27, 33, 42, 43]. Older patients must face issues like co-morbidities, physical limitations and social isolation which can lead to two contradictory outcomes—either non-adherence or better awareness of their limits and so closer attention to drug regimens and medical follow-up [27, 47, 48]. Recipients

with greater social support are more than twice as likely to be adherent [3]. Social support implies emotional support (love, friendship), instrumental support (food preparation, daily help), informational support (in a stressful situation), and appraisal support (information to help self-evaluation) [3]. The better the relational quality, the better the adherence [59–61].

As time passes after transplant, the risk of non-adherence increases. Three stages of adaptation have previously been described: (1) During the first year after transplant patients are hyper-vigilant and closely followed by physicians (2) After the first year recipients get used to their medication, experience less anxiety and become more relaxed (3) after 3 years, patients become exhausted with continuous treatment and monitoring and adhere less [49]. However, no consensus exists. In their review, Williams et al. indicated that 6 months after transplant, 70% of recipients increasingly tended to skip doses [58] but we observed non-adherence from the third month post-transplant [54]. We also found a relationship between type of donor and medication adherence. Patients receiving a kidney from a living donor could be assumed to be more adherent, but surprisingly, our review revealed the opposite. Denhaerynck et al., observed that unrelated living-donor recipients and deceased-donor recipients had similar adherence rates, suggesting that relatedness could account for differences [62].

Drug regimens and their complexity must be considered due to: (1) pill characteristics (large size, bad smell or unpleasant taste) (2) dosage and scheduling (difficulty in taking medication on time, delay between 2 drugs to avoid drug–drug interaction, recurrent changes in treatment, varying dosages…) (3) side effects (4) inadequate access to physicians and pharmacies, thus difficulty in obtaining prescription renewals on time [5, 7, 15, 50, 53]. In renal transplant, morning intake is better adhered to than evening intake which may account for the significant improvement in adherence rates with the once-a-day formulation of tacrolimus [43, 56, 63–65]. According to Griva et al., non-deliberate forgetfulness occurs mostly when patients find themselves in non-routine or competitive situations (work/social/other activities) or when medical regimens are changed. Forgetfulness usually means not taking medication on time. The main reasons for intentional non-adherence are complexity of regimen (number of prescribed medications/dose/scheduling) [15] and side effects which incite patients to postpone drug intake or reduce doses. These elements can increase the variability of calcineurin inhibitor blood levels which is predictive of non-adherence [66].

Patient-related factors influence attitudes. Based on beliefs, patients can be categorized into different types: accidental non-adherent (non-deliberate forgetfulness), invulnerable non-adherent (casualness towards medication) and decisive non-adherent (self-decider despite medical recommendations) [6]. Patients generally agree that they are responsible for their health status. If they are concerned by the disease, believe it has serious consequences on their well-being and trust in the benefits of the treatment, they will adhere [6, 47].

Psychological disorders emerge as predictors of non-adherence [33, 47, 57, 67]. Anxiety is caused by fear of death, guilt for desiring an organ from a deceased donor, and concerns over changes in life-style [68]. Depression is related to a loss of social support, inability to engage daily activities, dietary restrictions, and financial difficulties [69]. Modifications in cognitive functions or asthenia can also lead to depressed moods and consecutively non-adherence. Such disorders can be treated effectively to enhance the quality of life, an essential factor if adherence is to be improved [15, 33, 57].

Nevertheless, these results must be interpreted with caution as misuse of the standard definition of adherence has resulted in much confusion over measuring it. No perfect measure exists in clinical routine to detect or foresee non-adherence. Many authors have failed to consider drug-taking as a dynamic process that fluctuates over time and among individuals; insufficiently powered studies have resulted in low-quality results; cross-sectional designs have largely contributed to these. It is therefore difficult to reach a consensus on the extent of deleterious consequences due to non-adherence. More studies are needed on the impact of health care systems, health care teams or providers on the incidence and outcome of non-adherence in kidney recipients [16].

This review has limitations: studies may have been missed due to search terms, more studies with insignificant rather than significant results may have been published, only one reader completed the sorting of publications and we were unable to perform a meta-analysis.

Since no recommendations exist to determine which combination of objective and subjective measures would most accurately predict non-adherence, more than one approach is required. A combination of self-reports and other methods offers a higher level of sensitivity and specificity [16]. The Scale to Immunosuppressive drugs (BAASIS) and the Immunosuppressant Therapy Adherence Scale (ITAS) seem to be the 2 main self-reports available but they target non-adherence behaviors towards immunosuppressants and are less accurate in identifying non-adherence to the overall medication regimen. The Compliance Evaluation Test questionnaire is derived from the 4-item Morisky scale previously used in transplant and is useful in detecting the latter [5, 70]. To assess patient-related factors such as behavior, beliefs or satisfaction, several questionnaires exist but only 3 are mainly used in

transplant: the Theory Planned Behavior (TPB) questionnaire [17, 69], the BMQ questionnaire [3, 15, 17, 46], and the SATMED-Q questionnaire [17, 71]. Depression and anxiety can be detected during clinical observation, if the patient has a prescription for anti-depressants and/or benzodiazepines, or through self-reports. The Beck Depression Inventory (BDI) and Hospital Anxiety and Depression (HAD) seem to be the most widely-used self-reports.

All these findings suggest however that further studies are needed to establish guidelines to measure adherence. Another unresolved issue is the number of questionnaires available and their possible unreliability in the field of transplant.

Conclusion

Risk factors for non-adherence can be classified into five categories as follows: 1. Socio-demographical factors (age below 50, male gender, low social support, unemployment, poor education), 2. Disease-related factors (more than 3 months after transplant, living donor, re-transplant, more than 6 co-morbidities), 3. Drug-related factors (more than 5 drugs/day, more than 2 intakes/day, cyclosporine treatment), 4. Patient-related factors (negative beliefs, negative behaviors and negative satisfaction), and 5. Psychological factors (depression and anxiety). These factors should be regularly screened to detect a risk of non-adherence as early as possible. Consequently, a standardized framework taking into account the fact that adherence is a dynamic process, is required. A lot of approaches exist but self-reports which are easy to use in routine practice remain the cornerstone of adherence assessment, although their reliability is still questionable. Models based on objective data, such as drug exposure, could provide a basis for further studies.

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