

Adherence to immunosuppressor medication in renal transplanted patients

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timing, wrong dose and/or wrong pill, but may also refer to missing appointments, not booking appointments, not doing blood work, not returning calls and/or refusal to follow the treatment regimen. In renal transplantation, adherence to immunosuppressive medication is a fundamental requisite in order to preserve graft function, since non-adherence is one of the main causes for late acute rejection, incomplete recovery after rejection treatment, chronic graft dysfunction, graft loss, and death. Transplantation failure due to treatment non-adherence is economically, socially, ethically and morally unjustifiable. This is a very prevalent issue: in some studies, its incidence is as high as 70% of patients. The self-reported nonadherence levels found in certain studies, including those performed immediately after transplantation show the need for early and continued intervention after kidney transplantation in order to maximise adherence and consequently clinical outcomes. There is not a single method to assess non adherence, thus combining several measures increases diagnostic accuracy. Electronic monitoring with a microdevice that records each time a pill bottle is opened is considered the "gold standard" for measuring adherence, but self-report at a confidential interview was the best measure of adherence. Thus non-adherence risk can be effectively assessed using clinically available assessment tools. Medication Adherence Scale, Brief Medical Questionnaire, Immunosuppressant Therapy Adherence Scale, Immunosuppressant Therapy Barrier Scale, Long-Term Medication Behavior Self-Efficacy Scale and Simplified Medication Adherence Questionnaire are some of the self-reported questionnaires. There are multiple factors associated with non-adherence in immunosuppressant therapy: Younger patients (adolescent, especially), poor health coverage, poor social support, unmarried, no family, non-Caucasian, immigrant, lower income, lower socioeconomic class, greater parental distress and lower family cohesion; complex medical regimens, higher number of drugs, longer time after transplant, toxicity, side effects, poor tolerance to medication, higher number of physicians involved, poor provider-patient rapport; psychological

Abstract

Non-adherence is a priority public health concern. Non-adherence means not taking medications, missing medications, taking too much, not taking enough, wrong

(dependency, high levels of anxiety and hostility, poorer behavioral functioning and greater distress in children) and psychiatric (depression) illnesses, low self-efficacy with medicine intake, perception of immunosuppressive therapy as not been necessary to preserve kidney function, forgetfulness, rebelliousness, poor perception of health, poor satisfaction, low Health-related Quality of life, addictions, lack of coping strategies and avoidance behavior; patient morbidity: comorbidity, receiving a transplant from a live donor, retransplantation, and non-insulin-dependent diabetes. The most frequent strategies to promote medication-taking must focus on modifiable risk factors. Reasons for non-adherence are complex and diverse and any successful intervention aimed at improving adherence must be multidimensional. Although effective intervention strategies are needed to improve immunosuppressant therapy adherence, few intervention studies have been conducted in the adult renal transplant population. In this study, we perform an exhaustive review of the different strategies reported in the literature. A number of key reasons for non-adherence are also provided.

Key words: Adherence; Transplantation outcomes; Renal transplantation; Immunosuppressive medication; Health-related quality of life

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Core tip: Non-adherence is a priority public health concern. In renal transplantation, adherence is crucial to preserve graft functioning. Non-adherence rates of up to 70% of patients, including immediately after transplantation demonstrate the need for early and continued interventions after transplantation to maximise clinical outcomes. To increase the diagnostic accuracy of non-adherence, several measures must be combined. Multiple risk-factors exist. The strategies to foster medication-taking must focus on modifiable risk-factors and be of multidimensional nature. The strategies reported in the literature, some keys to understand non-adherence, and a few intervention studies are reviewed in this paper.

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INTRODUCTION

Non-adherence is a priority public health concern. Following the World Health Organization, the definition of adherence would be: "the extent to which a person's behavior-taking medication, following a diet, and/or executing lifestyle changes-corresponds with agreed recommendations from a health care

Table 1 Health effects of non-adherence^[2]

Increased morbidity
Treatment failures
Exacerbation of disease
More frequent physician visits
Increased hospitalizations
Decreased HRQoL
Decreased survival
Death
Economic impact: lost wages, sick time

HRQoL: Health-related quality of life.

provider"^[1]. According to cochrane review^[2]: (1) adherence is intended to be a non-judgmental term, and a statement of fact rather than blame of the prescriber, patient, or treatment; (2) compliance infers conformity to medical or health recommendations; and (3) concordance is a consensual agreement about treatment taking established between patient and practitioner.

Non-adherence means not taking medications, missing medications, taking too much, not taking enough, wrong timing, wrong dose, and/or wrong pill, but also may refer to missing appointments, not booking appointments, not doing blood work, not returning calls, and/or refusal to follow the treatment regimen.

Non-adherence implies major consequences. In Table 1, there is a list of health effects of non-adherence.

Furthermore this is a very prevalent problem. A cochrane review^[2] shows benchmark of non-adherence rates were: epilepsy 30% to 50%, arthritis 50% to 71%, hypertension 40% (average), diabetes 40% to 50%, oral contraceptives 8% and asthma 20%.

A complete review to update the results of randomized controlled trials of interventions to help patients follow prescriptions for medications for medical problems was achieved in January 2007^[3]. The authors' conclusions were: "for short-term treatments several quite simple interventions increased adherence and improved patient outcomes, but the effects were inconsistent from study to study with less than half of studies showing benefits. Current methods of improving adherence for chronic health problems are mostly complex and not very effective, so that the full benefits of treatment cannot be realized".

In a previous review by these authors, interventions for Medication Adherence in cochrane review Oct 2005^[2] can be seen in Table 2.

IMPORTANCE OF ADHERENCE/ NON-ADHERENCE AND RENAL TRANSPLANTATION

In renal transplantation, adherence to immunosuppressor medication is an indispensable requirement in order to preserve graft function. The concept of adherence

Table 2 Interventions categories^[2]

More instruction of patients
Counseling about target disease, compliance with therapy, side-effects
Automated telephone, computer-assisted patient monitoring and counseling
Manual telephone
Family interventions
Increasing convenience of care
Simplified dosing
Different formulations
Self-monitoring strategies
Reminders
Dose-dispensing units/charts
Appointments and refill reminders
Reinforcement or rewards for improved adherence in reduced frequency of visits
Crisis intervention
Direct observation
Lay health mentoring
Comprehensive pharmaceutical care
Psychological therapy

refers mostly to the compliance with the instructions regarding prescribed timing and doses. Adherence can be also assessed in other domains as blood work, clinical attendance, diet, exercise, and other healthcare requirements.

Some solid organ recipients do not take their treatment as prescribed, and thus they fail to reach the desired outcomes. Furthermore, this is one of the main cause of late acute rejection, incomplete recovery after rejection treatment, chronic graft dysfunction, graft loss, and death. It should be stressed that it is also a potential modifiable risk factor for poor outcomes. The negative consequences of non-adherence are numerous, and may complicate the management of the disease, due to the need of additional time, a reduction in the benefits of the treatment, a loss of medication cost-effectiveness, the need of higher doses or stronger medicines, intoxication and other undesirable effects, as well as an increase in sanitary costs, which translates into a loss of money at the expense of budget allocation for other health services.

Transplantation is the best renal replacement therapy in terms of health-related quality of life (HRQoL). According to some studies, HRQoL can be similar to that of the general population^[4]. Many studies confirm that improvement in HRQoL^[5-9], even in elderly patients^[10] or up to five different scenarios of transplant evolution^[11].

There also exist three meta-analyses which are in agreement with the evidence of an improved HRQoL after receiving a renal transplant: the first was carried out by Dew *et al.*^[5] with 66 articles and 6726 patients selected, another by Cameron *et al.*^[12] included 49 articles selected and, lastly, one by Tonelli *et al.*^[13], in which 110 studies are selected, comprised an astounding 1922300 patients. In fact, most of the studies reported a statistically significant improvement after transplantation with respect to the pre-transplant physical, mental (in over 70% of the studies equal to

or superior and the global HRQoL in almost 100% than that of the healthy population) and social dimensions of HRQoL. So there is a confirmation of the generalised clinical impressions of improvement, but the unpublished studies without findings of improvement in HRQoL after renal transplantation, and the variability of the case-mix variables in the different samples and groups of treatment, should counsel prudence.

Renal transplantation improves considerably the patient's autonomy, who does not depend on a machine, and reduces morbi-mortality, since the risk of death is lower in transplanted patients than in those on waiting lists^[14]. Nevertheless, it must be noted that not all the required transplantations can be performed due to the lack of organs, which leads to waiting lists for kidneys. Yet another aspect that has to be taken into consideration is the yearly per-patient cost of dialysis (around 50000 EUR per year and patient on average), as opposed to the cost of transplantation. Even though the cost of the first year is roughly similar to that of dialysis, it is reduced to 10000 EUR per year from the second year post-transplantation^[15].

All these reasons make the later failure of transplantation due to non-adherence to treatment economically, socially, ethically and morally unjustifiable.

PREVALENCE OF NON-ADHERENCE IN RENAL TRASPLANTEES

Despite the devastating consequences of non-adherence, including a decrease of HRQoL, an increase in sanitary costs, the need for dialysis, an increase in morbidity and mortality, *etc.*, a study to determine the percentage of non-adherent patients carried out in Italy^[16] with 7206 patients revealed that 267 non-adherent patients lost the graft. The study identified three main profiles or non-adherent transplanted patients: "accidental" non-adherents (47%), which are those who forget to take their medications from time to time; "invulnerable" non-adherents (28%), which believe they do not need to take immunosuppressors regularly, and "decisive" non-adherents (25%), who decide which treatment to take for themselves.

Rosenberger *et al.*^[17] find a 54% rate of non-adherence and Chisholm *et al.*^[18] refer non-adherence ranges between 5% and 68%. Other authors^[19] who used the "gold standard" measure (electronic monitoring) in a cohort of 58 renal transplantees found that 12% of the patients forgot their medication at least 20% of the days, and 26% forgot to take their medication at least 10% of the days. Denhaerynck *et al.*^[20] present a prevalence range of adherence between 2% and 67% and a weighted prevalence of 28% in a literature search of 38 articles measuring non-adherence. A cross sectional study^[21] in a Swedish population with 250 renal transplant recipients showed only 46% never failed to follow the medical treatment with respect to drug intakes, dosage or timing. Timing

was the most frequently reported deviation (48%). Sixteen percent of them had failed taking at least one dose of the prescribed immunosuppressants during the previous four weeks. Four individuals had reduced the prescribed doses. Only one reported taking a "drug holiday". Nine participants reported stronger concerns than the need for immunosuppressive medication. In a cross-sectional sample of 218 patients recruited in London, United Kingdom (1999-2002), adherence was measured. The results were: low intentional non-adherence (13.8%) although 62.4% admitted unintentional non-adherence and 25.4% presented sub-target immunosuppressant levels^[22]. As evidenced, non-adherence is common in kidney transplantation, especially in younger patients, but in older patients too. A project^[23] was undertaken to examine outcomes of medication adherence in 37 renal transplant recipients. The Medication Event Monitoring System was implemented for one year. Eighty-six percent of the participants were non-adherent with medications. Similar percentages of non-adherence are seen in children and adolescent patients. For instance, a cross-sectional study showed that expression of Quality of Life of the adolescents was satisfactory, but parents told serious problems as a 75% of them were non-adherent with their immunosuppressive drugs and had other problematic health behaviors (smoking, illicit drug use, dietary non-adherence, and suboptimal exercise levels)^[24].

The self-reported nonadherence levels found in studies, including immediately after transplantation prove the need for early and continued interventions after kidney transplantation in order to maximise adherence and consequently clinical outcomes^[25].

However, caution must be exercised since in a prospective, non-interventional cohort, French study with a total of 312 kidney transplant recipients from eight French transplantation centers, it was observed that physicians underestimated the prevalence of adverse events when compared to patient self-reporting^[26].

RELATIONSHIP BETWEEN NON-ADHERENCE AND CLINICAL OUTCOMES

Another issue medical literature reveals is the relationship between non-adherence and clinical outcomes and the costs of transplanted renal patients. Non-adherence to immunosuppressive medication is in fact one of the main causes of transplant failure, and it may potentially explain why kidney survival does not improve as expected despite the development of new immunosuppressors. Data clearly show how graft survival is significantly worse in non-adherent patients. A meta-analysis by Butler *et al.*^[27] of 325 studies published between 1980 and 2001 to measure the frequency and impact of non-adherence in renal failure revealed that non-adherence to immunosuppressants

is a major cause of renal transplant failure. In cross-sectional studies ($n = 15$), a median (interquartile range) of 22% (18%-26%) of recipients were non-adherent. Cohort studies ($n = 10$) indicated that non-adherence contributes substantially to graft loss; a median of 36% (14%-65%) of graft losses were associated with non-adherence. Meta-analysis of these studies showed that the odds of graft failure increased sevenfold (4%-12%) in non-adherent subjects compared with adherent subjects. This is in keeping with the data compiled by other authors^[28] who, in a study featuring 24.5% of non-adherent patients (7.7% "casual" non-adherents and 16.8% "severe" non-adherents), proved that the most severe non-adherent recipients experienced a higher number of acute rejection episodes and higher graft dysfunction. In a prospective study, Vlamincx *et al.*^[29] studied one hundred and forty-six adult renal transplant recipients during a 5-year period in order to know differences between the incidence of late acute rejections and changes in serum-creatinine between compliers and non-compliers (22.6%) with immunosuppressive therapy after 1 year of receiving transplantation. Twenty-one point two percent of non-compliers patients had an acute rejection vs 8% in the group of compliers. Conclusion was that non-compliance in renal transplant patients is associated with a 3.2 higher risk for late acute rejections and a higher increase in serum-creatinine. Another randomized trial^[30] involving 150 kidney transplant recipients with a median follow-up of 8 years post-transplantation found that patient non-compliance seemed responsible for 45% (13/29) of observed graft failures, with 11 of these occurring after 36 mo. Non-compliance as a cause of graft failure may become more prominent as immunosuppression trials achieve longer-term follow-up.

In conclusion, non-compliance with immunosuppressive medications in renal transplant recipients results in higher rate of acute rejection episodes, allograft dysfunction, graft loss and patient death.

As for costs, another study^[31] examining the relationships between compliance with allograft outcomes and costs in 15525 renal transplant recipients showed that adolescent recipients aged 19-24 years were more likely to be persistently non-compliant than patients aged 24-44 years. Poor and fair compliant recipients were associated with increased risks of allograft loss compared to the excellent compliant recipients. Persistent low compliance was associated with a \$12840 increase in individual 3-year medical costs. Similar findings appear in pediatric patients: Chisholm-Burns *et al.*^[32], using data reported by the United States Renal Data System (USRDS), which contains Medicare prescription claims, suggested that greater adherence was significantly associated with longer time to graft failure ($P = 0.009$). Cleemput *et al.*^[33] examined economic evaluation by means of a Markov model and found that the mean cost per QALY

(Quality-Adjusted Life-Year) gained in adherent patients relative to non-adherent patients was eur 35021 per QALY. A specialty pharmacy program (in addition to medication dispensing, it includes adherence and clinical management programs, patient education, and counseling services provided by transplant pharmacology experts) was implemented by Tschida *et al.*^[34] and it was associated with lower transplant-related medical costs (the mean transplant-related medical cost was 42% lower in the specialty pharmacy program group: \$5960 vs \$8486; $P=0.04$), as well as higher transplant medication adherence within the first year of evaluation.

HOW TO MEASURE ADHERENCE IN RENAL TRANSPLANTATION PATIENTS

When it comes to assessing adherence, Butler *et al.*^[27] point out in their meta-analysis that only 2 of the 325 studies published from 1980 to 2001 used the "gold standard" measure of electronic monitoring with a microdevice that records each time a pill bottle is opened. Currently, this is the most accurate measure for prospective studies, since transversal studies used to employ self-report questionnaires. Butler *et al.*^[35] also studied the sensitivity and specificity of these measures in comparison with electronic monitoring. Their conclusion was that self-report at a confidential interview was the best measure of adherence for the detection of both missed doses and erratic timing of medication. Thus non-adherence risk can be effectively assessed by means of clinically available assessment tools.

The clinical methods more frequently used are self-reported questionnaires and interviews, clinician rating, plasma levels of immunosuppressants and their variability, pill counts, refill records, clinical outcomes, and biological and chemical markers ("white coat adherence").

For instance, the variation of serum drug levels was employed as a potential objective tool to monitor medication nonadherence. Hsiao *et al.*^[36] studied variations of tacrolimus and mycophenolic acid trough levels in 46 pediatric patients who underwent renal transplantation between 2002 and 2003 from 1 to 12 mo post-transplant, and standard deviation (SD) and percent coefficient of variation (%CV) were calculated. The tacrolimus %CV seems to be a useful and better marker, compared with SD alone.

The best methods for using self-report and trough levels to predict non-adherence likely differ based on the medication for which adherence is being assessed^[37]. Medication Adherence Scale^[38], Brief Medical Questionnaire^[39], Immunosuppressant Therapy Adherence Scale^[40], Immunosuppressant Therapy Barrier Scale^[41], Long-Term Medication Behavior Self-Efficacy Scale^[42] and Simplified Medication Adherence Questionnaire^[43] are some of the self-reported questionnaires.

naires.

On the other hand, 73 older adult renal transplanted patients expressed their perceptions with the Medication Event Monitoring System [MEMS^(®)] TrackCaps for 12 mo. They perceived that the MEMS had a neutral effect on their medication-taking routine (65%), believed it was practical (56%), and could not describe any instances in which using the MEMS was difficult (56%). No significant difference in medication adherence was found between those who perceived the MEMS' influence negatively/neutrally and those who perceived the MEMS' positively^[44]. However Israni *et al.*^[45] also utilized microelectronic cap monitors to determine the association of adherence with a single immunosuppressive medication and kidney allograft outcomes post-transplantation in a prospective cohort study (243 patients from eight transplant centers) and conclusion was non-adherence was not associated with kidney allograft outcomes. Other more sophisticated electronic monitoring systems are being used but there is not sufficient experience yet. For instance, the Ingestible Sensor System, a novel technology for directly assessing the ingestion of oral medications and treatment adherence that provides highly reliable measurements of intake^[46].

A general conclusion for achieving a diagnosis of non-adherence would be that combining measures increase diagnostic accuracy, and it's relevant for clinical and research purposes^[47].

DETERMINANTS AND FACTORS INVOLVED IN NON-ADHERENCE

Regarding the determinants which lead to medication non-compliance, there are many, including ignorance, forgetfulness (awareness of memory impairment significantly affected adherence to immunosuppressive drugs^[48] and following Schmid-Mohler *et al.*^[49] "forgetfulness is the most powerful barrier against adherence. Intention to adhere plays a minor role in non-adherence in renal transplant recipients"), lack of understanding of the instructions provided by the health practitioner, disbelief or doubts concerning the need or benefits, treatment costs, unpleasant side effects, rebelliousness, presence of psychiatric illness, depression, comorbidity, medication tolerance, number of drugs^[50] and the complexity of the treatment, poor patient-physician communication which explains the "center effect"^[51], the lack of social support and not having family^[51,52].

According to studies on factors which may condition adherence, it seems that being female (or having a male partner, or being unmarried^[53,54]), a poor perception of one's health and a poor satisfaction predict a low HRQoL and low adherence^[55]. There also appears to be a relationship with time from the date of transplantation, both in the case of recent transplantation^[18] and the longer its duration^[28,54], as well as in cases of retransplantation^[54].

One obvious factor is younger age, as confirmed

in several studies; furthermore, Dobbels *et al.*^[56] found 36 studies, with a prevalence of non-adherence of 31.8%. Adolescents had more risk than younger patients and they had a 44% of all graft losses and a 23% of late acute rejection episodes associated with non adherence. Dew *et al.*^[57] found 61 papers in a meta-analysis in pediatric solid organ transplantation. Non-adherence to clinic appointments and tests was at 12.9 cases per 100 patients per year, the immunosuppression non-adherence six cases and other (substance use restrictions, diet, exercise, *etc.*) 0.6 to 8 cases. Age, family functioning (parental distress and family cohesion), and the child's psychological status significantly correlated with poorer adherence. Similar findings were obtained by Gerson *et al.*^[58].

Other important factors are socioeconomics, such as lower income^[18,51,54], lower socioeconomic class^[28] and poor socioeconomic background^[51] as well as addiction^[28] and psychiatric illnesses^[28] such as depression^[27,54,59] and higher stress levels^[54]. Other, more debated factors include lower education levels, receiving a transplant from a live donor^[27], non- insulin-dependent^[54] and to what extent may be related with a lower adherence to the immunosuppressive treatment.

On the other hand, there are several reviews on the determinants and factors associated with non-adherence. While reviewing the literature, Jindal *et al.*^[60] found that out that of all renal transplantees, the patients with a higher risk of non-adherence were younger, women, single and non-Caucasian, in addition to patients receiving a transplant from a live donor, those who had been transplanted for more time and those with a previous transplant. They also discovered that patients exhibiting emotional issues such as anxiety, hostility, depression, distress, lack of coping strategies and avoidance behavior also showed a higher risk of non-adherence after renal transplantation.

Loghman-Adham^[51] also point as factors some identified in certain studies on poor adherence, such as: frequent doses (regarding this, several works prove the beneficial effect on self-reported adherence and treatment satisfaction in renal transplant patients taking tacrolimus once daily vs twice daily^[61-64], including in the long-term^[65]), the patient's perception of the benefits of the treatment^[27], poor provider-patient rapport, lack of motivation, belonging to a lower social class, lack of familiar or social support and being younger.

PSYCHOLOGICAL FACTORS, UNDERSTANDING NON-ADHERENCE, REPRESENTATIONS OF THE DISEASE

How can non-adherence in renal transplantation patients be properly understood? Renal transplantation is a therapy which comprises a set of beliefs and issues. In order to provide meaning and answers to the disease, patients create their own models or "representations"

of the disease, which may incorporate doubts or false beliefs about the disease, the benefits of the treatment and the adherence to immunosuppressive medication. Different representations may have different effects on clinical outcomes, since they modulate the relationship between the patient and the disease. In recent years, the study of the role of beliefs about the disease and how they may impact health-related outcomes has become one of the most productive areas within Health Psychology. One of the most rewarding theoretical frameworks is the self-regulatory or "common sense" model proposed by Leventhal and his group^[66]. Leventhal formulated a model which emphasizes the role of the theories the patient develops around his or her own health status; they are called "common sense" theories, as opposed to the scientific theories which direct the performance of the practitioner, and whose value lies in their ability to determine the behavior of the individual^[67,68]. The model stems from the understanding of individuals as active "troubleshooters" who organize the processing of perceptive and conceptual information about threats against health, self-regulated by a feedback system^[69]. Thus, initially, people process external information, such as a message from a health professional, or internal, such as the detection of a symptom, and elaborate a cognitive representation of the issue, as well as the associated emotions. As a second step, plans of action or coping procedures (such as seeking support or taking medicines) are developed. Lastly, the third step entails assessing the consequences which may affect the previous stages and then modify accordingly any subsequent episodes against future health threats. The potential practical usefulness lies in the possibility of handling representations in order to modify the impact of these cognitive/emotional representations of the disease on the health-disease outcomes: physical condition, stress, psychological well-being, social functioning, *etc.*, and thus this may be a chance to identify the representation as a means to intervene and enable adaptation and recovery. There are very few studies which properly convey the cognitions of renal transplantation patients and their behavior related to medication and rejection. Data yielded by cognitive behavioral models stress the importance of representations on the disease regarding the persistence of a given disorder or upset. Terminal chronic renal failure is associated with a remarkable loss of personal control and the lifelong challenge of modifying behavior^[70]. Regarding compliance in chronic diseases, Phatak *et al.*^[71] state that the beliefs of patients about medication are associated to non-adherence. There are associations between certain beliefs, such as perceiving more uncomfortable side effects and that the patient is taking more medicines than needed. Beliefs about medication explain on their own the 22.4% of variance in chronic diseases. Along the same lines, other authors have recently published a study in which perceptions of the disease explain between 6% and 26% of variance in psychological distress averages, and

disease strategies explain between 12% and 25%. The more symptoms patients have, which they attribute to the disease, and the greater emotional load they provoke, the higher the psychological distress and the less they use adaptative strategies, such as focusing on problems and easing their emotions.

However, to think that one has a more personal control over the disease and the use of adaptative coping strategies, such as positive reinterpretation and growth, are associated with reduced distress levels. It appears that coping strategies act as mediators between the perceptions about the disease and the outcomes. These findings support the role disease perceptions and coping strategies play when explaining the levels of psychological distress in patients^[44].

It would also appear that labeling a disease as chronic is associated with a reduction in the belief of personal control and treatment efficacy, as well as an increase in the perception of the consequences of the disease on daily functioning. Besides, a lower coherence with respect to the disease is linked to an increase in psychological distress. Resorting to psychoeducation before implementing a therapy or treatment helps patients to better understand their disease and the treatment, and it is also effective in reducing psychological distress and may possibly improve future well-being^[72]. Table 3 shows a summary of non-adherence risk factors.

Relationship between disease representations, HRQoL, psychological factors and adherence

Only a few studies have assessed the psychological factors which may be having an impact on patients' adherence. Butler *et al.*^[19] tried to analyze the relationship between disease representations, HRQoL, depression and adherence. They found that factors more associated to noncompliance are a lesser belief in the need for medication and receiving a transplant from a living donor. Suffering from depression was also common, but it was not strongly linked to non-adherence. These authors share and confirm the worrisome situation of finding a higher rate of non-adherence in renal transplantees from living donors because of the emphasis nephrologists are currently putting on spreading the use of this technique. A relatively recent study^[73] informed that younger patients, those who perceived less autonomy when dealing with the treatment, resorted to more active coping strategies and those who perceived a higher degree of interference of the treatment with their normal lives exhibited a worse adherence to treatment. In addition, there is a relationship between disease representations and HRQoL in renal patients. Covic *et al.*^[74] found that the adaptation of a patient to a chronic disease is determined by their beliefs about the disease and about the treatment. Between 15% and 31% of the variance rate in Physical Component Summary and Mental Component Summary can be explained by three

dimensions of the disease representation: the perception of the evolution of the disease, personal control, and the emotional response to the disease. The HRQoL of these patients is the result of a complex interrelation of clinical and personal factors. We believe that the two key components of the self-regulation model (beliefs and strategies) do explain HRQoL outcomes of the patient and adherence to medication. Furthermore, the perceptual framework about disease perceptions may be useful to make explicit and understand the ideas patients have about the disease^[75].

After receiving a transplanted organ, patients live with the uncertainty and the fear their body will reject the organ and with the need of acquiring new strategies and resources to look after themselves, such as recognizing the signs and symptoms to avoid infections and rejection. This suggests that after transplantation and being discharged from hospital, the patient has to carry on with his or her life as if having a chronic disease. The success of most therapies always depends to a great extent on a patient's disposition; thus, managing the active implication of the patient is of utmost importance. Managing the disease is a process for which the specialists and the patients are all responsible. If patients forget to follow their prescribed treatment, refuse the medication or, conversely, self-medicate, this may limit or prevent the proper management of the disease, which in turn will always compromise the benefits of the treatment.

STRATEGIES FOR MINIMIZING NON-ADHERENCE IN RENAL TRANSPLANTATION

Intimately linked to the previous section on determinants and factors, the most frequent strategies to promote medication-taking need to focus on the modifiable risk factors. Reasons for non-adherence are complex and a successful intervention to improve adherence must be multidimensional. Although effective intervention strategies are needed to improve immunosuppressant therapy adherence, few intervention studies have been conducted in the adult renal transplanted population. Chisholm-Burns *et al.*^[76] implemented a randomized controlled trial of a patient-specific behavioral contracts intervention to improve immunosuppressant therapy adherence among adult with a renal transplantation. Researchers developed a toolbox that included simple, practical, accessible mechanisms and strategies to improve immunosuppressant therapy adherence. One hundred and fifty renal transplant patients were enrolled in the study: the 76 in the intervention group had higher adherence than 74 in control group. Furthermore, 76.1% of patients in the intervention group compared with 42.7% in the control group were not hospitalized during the 1-year study period, resulting in cost savings. Thus, evidence supports

Table 3 Factors associated with non-adherence to immunosuppressive therapy

Age of patients: Younger (specially adolescent) and older patients (> 55 yr)
Gender: Male (or female), not having a female partner
Socioeconomics and cultural: Poor health coverage, poor health access, costs of treatment, difficulty in transportation, poor social support, unmarried, no family, non caucasian, immigrant, lack of general education and specific education about renal transplantation, lower income, lower socioeconomic class, poor socioeconomic background, greater parental distress and lower family cohesion in family functioning
Medication: Complex medical regimens, higher number of drugs, longer post-transplant, toxicity and side effects, poor tolerance of medication, higher number of doctors, poor provider-patient rapport, patient implicitly seen as defaulter
Psychological: Psychological (dependency, high levels of anxiety and hostility; in children, poorer behavioral functioning and greater distress) and psychiatric illness (depression), low self-efficacy with med intake, perceptions of immunosuppressive therapy as not needed to keep the kidney, significant positive relationship between pre-tx non-adherence and post-tx non-adherence (past behaviour predicts future behaviour), evolution of disease is a matter of chance, forgetfulness, rebelliousness, poor perception of health, poor satisfaction, low health-related quality of life, addictions, lack of coping strategies and avoidance behavior
Patient morbidity: Comorbidity, receiving a transplant from a live donor, retransplant, non-insulin-dependent diabetes
Other: No research, opportunities for improving adherence through optimizing the health care system or training the health care work remain hidden

using behavioral contracts as an effective adherence intervention that may improve healthcare outcomes and lower costs. Through a randomized controlled trial design, Russell *et al.*^[77] screened 30 adult renal transplant recipients for medication non-adherence using electronic monitoring. Fifteen non-adherent participants were randomized to receive either a 6-mo continuous self-improvement intervention or attention control management. The mean medication adherence score for the continuous self-improvement intervention group ($n = 8$) was statistically significantly higher than the attention control group's ($n = 5$) mean medication adherence score. Participants' perceptions of the intervention were highly favorable. De Bleser *et al.*^[78] reviewed 12 intervention studies and found that only 5 used randomized control designs. No single intervention was superior, so authors concluded that a combination of interventions with a team approach may be the most useful long-term strategy. O'Grady *et al.*^[79] propose multidisciplinary insights too. A good minireview is that by Prendergast *et al.*^[80]. Gordon *et al.*^[81] found the barriers were: forgetting to refill prescriptions (13%), changes in prescriptions or doses (13%), being busy (10%), forgetting to bring medicines with them (10%), and being away from home (10%). Thus the strategies to avoid non-adherence were: having a schedule of medication-taking (60%), using devices as pillboxes (42%), bringing medicines with them (34%), distributing pills according to routine (32%), and using other people to remind them (26%). There are findings which suggest that strategies using social support to avoid forgetfulness and other to improve affectionate and instrumental support related to daily routine may be useful tools^[52]. And more particularly the prevalence and consequences of cost-related immunosuppressive medication non adherence among kidney transplant recipients have now been documented (continuous insurance coverage for outpatient immunosuppressive medications remains a major issue)^[82]. As for the "how" these strategies may be implemented, new technologies are already being used. For instance, mobile phone based remote monitoring of medication

adherence improves long-term graft outcomes in kidney transplants. This is a relatively no expensive technology and it may offer a close patient monitoring in a non-intrusive manner. Some recent studies demonstrate that kidney transplant recipients have a positive overall attitude toward mobile phone and they were comfortable with the idea of being monitored using it and confident that their privacy can be protected^[83]. Other paper^[84] shows that a new smartphone application in order to support drug adherence, was used by 11688 chronically ill users with a wide range of diseases over a longer period of time. Thirteen percent (292) had a previous history of transplantation and the results were positive.

However, to sum up, there are no definitive methods in place to properly measure adherence, it is not well studied and there are no single sufficiently supported effective interventions.

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