Increased Prevalence of Gastrointestinal Symptoms Associated with Impaired Quality of Life in Renal Transplant Recipients

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Background. Immunosuppressive therapies have been associated with gastrointestinal (GI) side effects, which may impair health-related quality of life (HRQoL).
Methods. In this survey, 4,232 renal transplant recipients from Denmark, Finland, Norway, and Sweden completed the Short-Form 36 (SF-36) questionnaire and the Gastrointestinal Symptom Rating Scale (GSRS). SF-36 scores were compared with country norm values. Multiple logistic regression analysis was used to identify immunosuppressants associated with GI symptoms.
Results. The prevalence of troublesome GI symptoms (GSRS>1) was 83% for indigestion, 69% for abdominal pain, 58% for constipation, 53% for diarrhea, 47% for reflux, and 92% for any GI symptom. Compared with the general population, HRQoL was most commonly meaningfully impaired in the general health dimension (53% of patients). The presence and severity of GI symptoms were associated with worse HRQoL. Tacrolimus showed a significant association with diarrhea (odds ratio [OR]: 1.7; 95% confidence interval [CI]: 1.4–2.0) and constipation (OR: 1.3; 95% CI: 1.1–1.6), and sirolimus with indigestion (OR: 2.9; 95% CI: 1.0–8.1) and abdominal pain (OR: 2.2; 95% CI: 1.1–4.4).
Conclusions. GI symptoms are associated with impaired HRQoL in the renal transplant population. Managing GI symptoms by careful choice of immunosuppressants should be a focus for improving HRQoL in renal transplant recipients.

Keywords: Kidney transplantation, Immunosuppression, Health-related quality of life, Gastrointestinal, Adverse events.

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Advances in transplantation procedures and immunosuppressive treatments have increased 1-year kidney graft survival rates to over 90% (*1*). As a consequence of this success, maximizing health-related quality of life (HRQoL) for renal transplant patients is now emerging as a primary focus of research and clinical practice. Recent studies indicate that renal transplantation dramatically improves HRQoL for patients with end-stage renal disease (*2–5*). However, HRQoL and physical health in particular do not appear to be completely normalized in individuals with successful kidney grafts, and seem to remain constant in the years following transplantation (*6*, *7*).

Immunosuppressive treatments are known to cause a number of side effects that may be responsible for the remaining impairment in HRQoL experienced by patients after kidney transplantation (*8*, *9*). There has been some comparison of the HRQoL of patients taking different immunosuppressive treatment regimens. A small, prospective, randomized study indicated that ciclosporin monotherapy may lead to a higher degree of psychosocial well-being compared with conversion from ciclosporin–prednisolone to azathioprine–prednisolone (*10*). In another small study, no difference was found between patients given tacrolimus and those receiving ciclosporin in terms of physical and mental HRQoL (*11*).

Gastrointestinal (GI) side effects have commonly been reported in clinical trials of immunosuppressive agents (*12–15*). Larger, retrospective studies have confirmed this association in everyday practice (*16*, *17*). For example, in the United States, a retrospective study of 768 renal transplant patients treated with mycophenolate mofetil showed that 382 patients (49.7%) suffered from gastrointestinal complications within 6 months of transplantation (*18*). GI symptoms are known to impair HRQoL in the general population (*19–21*). However, very little is known about the specific effect that GI symptoms have on the HRQoL of renal transplant patients, particularly in everyday clinical practice and outside the United States. GI symptoms may play a role in the aspects of HRQoL that remain impaired after renal transplantation.

The aim of this survey was to determine the prevalence of GI symptoms among renal transplant patients and the HRQoL of these individuals compared with published data from the general population. The survey aimed to be as informative as possible by asking a large number of patients about their experiences using validated questionnaires. It also sought to uncover whether GI symptoms in particular impair HRQoL in renal transplant patients and whether their pres-

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ence and severity is influenced by the immunosuppressive treatments used.

METHODS

Patients

This observational cross-sectional survey assessed GI symptoms and HRQoL in renal transplant patients. In 2005, 6,067 postal questionnaires were sent to adult postrenal transplant patients in Denmark, Finland, Norway, and Sweden, via the renal transplant units in Århus, Helsinki, Herlev, Malmö, Odense, and Oslo. The source population included all patients who were alive, had a functioning graft, were over 18 years of age, and had received a kidney transplant at any of these transplant units. In Finland, only a very small number of patients receive their kidney from a living donor. Questionnaires were therefore not sent to these individuals because they may represent a very special group. The study was approved by the research ethics committee of each of the institutions involved.

Questionnaires

In order to assess quality of life, patients were asked to complete the Short-Form 36 (version 2) general health questionnaire (SF-36), which has a four-week recall period. Validated translations of the SF-36 in Danish, Finnish, Norwegian, and Swedish were used (*22–25*). The 36 items in the SF-36 are organized into eight dimensions: physical functioning, role-physical (role limitation as a result of physical difficulties), bodily pain, general health, vitality, social functioning, role-emotional (role limitation as a result of emotional difficulties), and mental health. The scores for each dimension are transformed to a 0- to 100-point scale, where higher scores reflect better functioning and well-being. The SF-36 has been extensively validated (*26*) and norm values are available for many countries, including those in this survey (*22–25*, *27*).

Subjective ratings of GI symptoms were obtained using the Gastrointestinal Symptom Rating Scale (GSRS). This questionnaire consists of 15 items asking individuals how bothered they are by gastrointestinal symptoms experienced over the previous week. Subjects respond using a seven-point Likert scale, which communicates the level of discomfort they experience such that 1=none, 2=minor, 3=mild, 4=moderate, 5=moderately severe, 6=severe, and 7=very severe discomfort. The 15 items are organized into five dimensions, which are diarrhea, indigestion, constipation, abdominal pain, and reflux. It has been validated (*28*) and has been successfully used to differentiate renal transplant patients with and without GI symptoms (*29*). Validated translations of the GSRS in Danish, Finnish, Norwegian, and Swedish were used.

A third questionnaire collected demographic data as well as information on the immunosuppressive treatments taken by renal transplant patients at the time of the survey. Patients were asked their sex, year of birth, civil status, the year of their transplantation, and whether the donor of their kidney was deceased or living. For the analysis, obviously incorrect data were set to "missing."

Analysis

Mean SF-36 scores in the survey population were calculated and compared with the norm values for their respective country (*22–25*). For Denmark and Norway, these were standardized by age and sex, and for Finland and Sweden according to age. A clinically meaningful impairment in HRQoL was defined as a reduction in SF-36 score that was statistically significant and at least five points lower than the relevant norm value. Increased HRQoL was defined as an increase in SF-36 score that was statistically significant and at least five points greater than the relevant norm value. A five-point difference in SF-36 score represents a 5% difference in health status, which has been shown to correspond to a clinically meaningful difference in HRQoL (*26*). The relationship between HRQoL and troublesome GI symptoms was investigated using generalized linear model analysis, looking at the effect of GSRS score on SF-36 score. The model selection was done by using Akaike's Information Criteria (AIC) and backward selection.

General data on the prevalence and severity of diarrhea, abdominal pain, constipation, reflux, indigestion, and overall GI symptoms in the renal transplant population were calculated from the GSRS. Predictors of GI symptoms (GSRS scores >1) in renal transplant patients were calculated by multiple logistic regression analysis. Models for each GSRS symptom were initially generated that included country, treatment, sex, marital status, donor, age, and time of transplant as variables. Nonsignificant variables were excluded and final odds ratios were adjusted for the variables included in the final model. ORs and 95% CIs were calculated with the absence of the studied factor as the reference category in each case. The residuals of the model were checked, and the Hosmer and Lemeshow goodness-of-fit test was used to evaluate the model. This gave nonsignificant probabilities for chi-squared distributions of each of the GSRS symptoms, indicating that the model's estimates fit the data.

RESULTS

Patient Demographics

In total, 4,232 patients returned questionnaires. This represented a response rate of 70% overall (4,232/6,067), 71% (735/1,035) in Denmark, 70% (1,366/1,961) in Finland, 70% (1,674/2,400) in Norway, and 68% (457/671) in Sweden. Table 1 presents demographic data on the renal transplant patients included in the survey. Respondents were representative of the source populations as a whole. In the Danish source population the median age was 52 ($\pm$11) years, 61% were male, and the median year of transplantation was 1998. In the Finnish source population, the mean age was 54 ($\pm$12) years, 60% were male, and the mean year of transplantation was 1997. In Norway, the mean age was 53 years, 64% were male, and the mean year of transplantation was 1997. In Sweden, the mean age was 51 ($\pm$14) years, 65% were male, and the mean year of transplantation was 1996. Overall, the survey population comprised a broad age range, from 19 to 88 years. Respondents in Denmark (mean age 51 years), were slightly younger than those in Finland (mean 55 years), Norway (mean 55 years), and Sweden (mean 54 years). The survey included some patients who had received very early transplants, although the majority were carried out in recent years. The year of transplantation means and standard deviations were similar among all Nordic countries. The only major difference between countries was the proportion of

TABLE 1. Demographic characteristics of the survey population

	Denmark n (%)	Finland n (%)	Norway n (%)	Sweden n (%)	All n (%)
Sex					
Male	428 (58.2)	781 (57.2)	1040 (62.3)	289 (63.2)	2538 (60.0)
Female	305 (41.5)	568 (41.6)	629 (37.7)	163 (35.7)	1665 (39.3)
Missing	2 (0.3)	17 (1.2)	5 (0.3)	5 (1.1)	29 (0.7)
Total	735	1366	1670	457	4232
Donor					
Deceased	531 (72.2)	1095 (80.2)	831 (49.6)	259 (56.7)	2716 (64.2)
Living	185 (25.2)	22 (1.6)	797 (47.6)	185 (40.5)	1189 (28.1)
Missing	19 (2.6)	249 (18.2)	46 (2.8)	13 (2.8)	327 (7.7)
Total	735	1366	1674	457	4232
Marital status					
Single	214 (29.1)	402 (29.4)	435 (26.0)	140 (30.6)	1191 (28.1)
Married/cohabiting	512 (69.7)	933 (68.3)	1229 (73.4)	312 (68.3)	2986 (70.6)
Missing	9 (1.2)	31 (2.3)	10 (0.6)	5 (1.1)	55 (1.3)
Total	735	1366	1674	457	4232
Age (years; mean±SD)	51.0±12.0	54.7±11.8	55.4±13.2	54.2±12.9	54.3±12.6
Transplant year (years; mean±SD)	1997±6	1997±6	1996±7	1997±7	1997±7

deceased donors. In Finland, a very small proportion of patients reported having received their graft from a living donor. In all Finnish cases, their latest, functioning transplant was from a deceased donor, so these answers were erroneous and were corrected to "missing" in the analyses.

Immunosuppressive Treatments

A range of immunosuppressive regimens had been prescribed (Fig. 1). Almost all patients received corticosteroids. Most patients received combination therapy of ciclosporin and prednisolone with either azathioprine (23%) or mycophenolate mofetil (20%). A high proportion of patients received a dual combination of ciclosporin and either prednisolone (16%) or mycophenolate mofetil (9%) and the next most frequent combination was prednisolone, tacrolimus and mycophenolate mofetil (7%). Less than 5% of patients received each of the other treatment combinations. The mean doses of immunosuppressants taken by patients were 1439.9 mg (SD: 662.9 mg) for mycophenolate mofetil, 197.4 mg (SD: 79.8 mg) for ciclosporin, 5.6 mg (SD: 3.4 mg) for tacrolimus, 5.3 mg (SD: 3.7 mg) for prednisolone, 913.9 mg (SD: 384.1 mg) for enteric-coated mycophenolate sodium (EC-MPS), 4.2 mg (SD: 2.4 mg) for sirolimus, and 2.0 mg (SD: 1.3) for everolimus.

Gastrointestinal Symptoms

The prevalence of troublesome GI symptoms (GSRS >1) was 83% for indigestion, 69% for abdominal pain, 58% for constipation, 53% for diarrhea, 47% for reflux, and 92% for any symptom (Fig. 2). Mean GSRS values were also high-

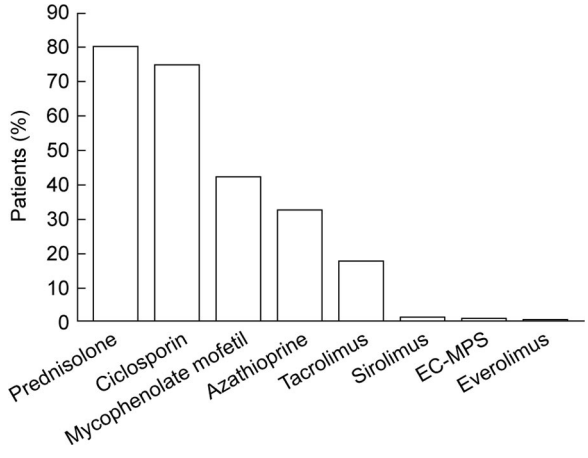

FIGURE 1. Immunosuppressive medications used by renal transplant recipients in the survey population (n=4232). EC-MPS, enteric-coated mycophenolate sodium.

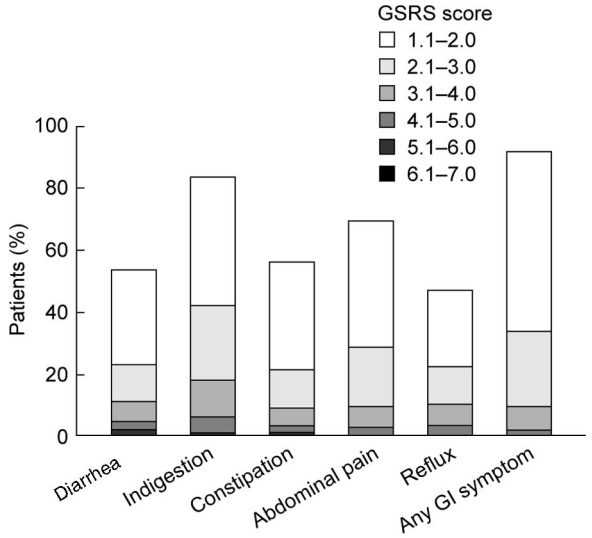

FIGURE 2. Prevalence and severity of GI symptoms in postrenal transplant patients, according to GSRS score.

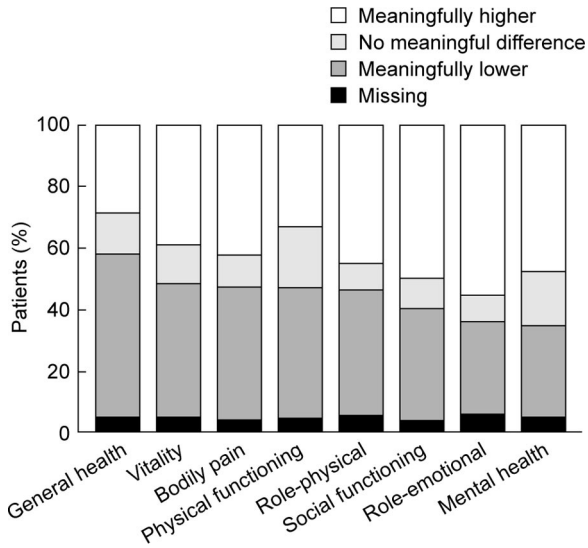

FIGURE 3. The prevalence of meaningfully higher and meaningfully lower SF-36 values for Nordic postrenal transplant patients in comparison with general population values (normalized for age or age and sex).

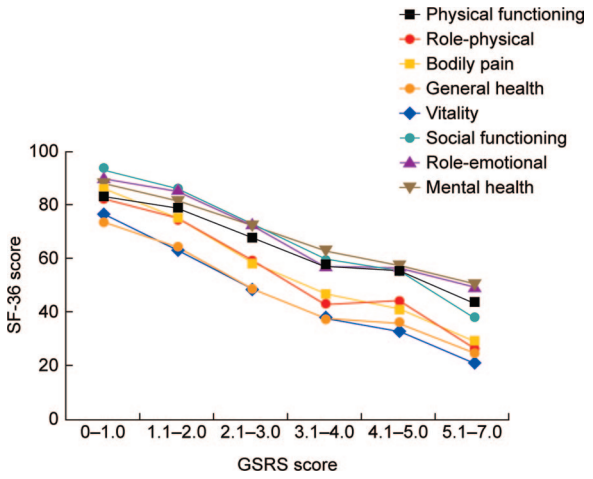

FIGURE 4. SF-36 values for postrenal transplant patients according to severity of any GI symptom.

est for indigestion (2.2; SD: 1.1), abdominal pain (1.9; SD: 0.9) and diarrhea (1.8; SD: 1.1). Mean GSRS values for constipation, reflux and any GI symptom were 1.7 (SD: 1.0), 1.7 (SD: 1.1), and 1.9 (SD: 0.8), respectively.

Quality of Life

A number of SF-36 dimensions were meaningfully impaired in renal transplant recipients in comparison with the general population. The SF-36 dimension most frequently impaired in renal transplant patients was general health (53.4%; 95% CI: 51.9–54.9%), followed by vitality (43.5%; 95% CI: 42.0–45.0%), bodily pain (43.2%; 95% CI: 41.8–44.8%), and physical functioning (42.1%; 95% CI: 40.6–43.6%; Fig. 3). For the other dimensions of the SF-36, 40.7% (95% CI: 39.2–42.2%) of renal transplant patients had meaningfully impaired HRQoL compared with the general population in the role-physical dimension, 36.7% (95% CI: 35.2–38.1%) for social functioning, 30.1% (95% CI: 28.7–31.4%) for mental health, and 30.2% (95% CI: 28.8–31.5%) for role-emotional (Fig. 3). Conversely, over half of patients had a meaningfully higher SF-36 score than the general population for role-emotional (55%), closely followed by social functioning (50%) and mental health (48%; Fig. 3). Renal transplant patients with GI symptoms (as identified by GSRS scores of >1) had lower SF-36 scores for all health dimensions, indicating impaired HRQoL. The greater the GSRS score, the more reduced the SF-36 scores, indicating greater HRQoL impairment with worse GI symptoms. The SF-36 dimensions of general health and vitality consistently had the lowest SF-36 scores (Fig. 4). Generalized linear model analyses showed that GSRS score had a statistically significant effect on SF-36 score for all dimensions (Table 2). All of the odds ratio values (in the case of general health, the multiple regression coefficient) pointed in the same direction and were of the same magnitude.

TABLE 2. Effect of GSRS score on SF-36 scores, obtained from generalized linear model analyses

SF-36 dimension	Generalized R^2	GSRS odds ratio	*P* value
Social functioning	0.173	2.87	<0.0001
General health	0.222	−13.77[a]	<0.0001
Bodily pain	0.212	2.79	<0.0001
Role-physical	0.234	2.62	<0.0001
Physical functioning	0.270	2.33	<0.0001
Mental health	0.168	2.71	<0.0001
Role-emotional	0.152	2.51	<0.0001
Vitality	0.230	3.21	<0.0001

For all analyses except general health, proportional odds models were fitted. For general health, a multiple linear regression model was fitted. For all SF-36 dimensions, the estimates were adjusted for sex, age, time since transplant, country and/or donor after a backward selection.

[a] Multiple linear regression coefficient.

Immunosuppressive Drugs Associated with Gastrointestinal Symptoms

Renal transplant patients taking tacrolimus, prednisolone, and sirolimus had a significantly increased likelihood of suffering from certain GI symptoms, as shown by multiple logistic regression analysis (Table 3). Most evident were the associations between tacrolimus and diarrhea, and sirolimus and indigestion/abdominal pain. Transplant patients taking azathioprine had a reduced risk of suffering from diarrhea, indigestion, and GI symptoms in general. None of the drugs was associated with reflux symptoms.

DISCUSSION

The vast majority of postrenal transplant patients reported troublesome GI symptoms in this survey. The GSRS is a validated questionnaire that enables our results to be compared with those from a number of other studies. The mean GSRS score for GI symptoms overall for the survey population was 1.9, which is higher than the score of 1.5 previously recorded for the general Swedish population (*30*, *31*). Similarly, for each individual symptom measured by the GSRS,

TABLE 3. Immunosuppressive treatments that were statistically significant predictors of GI symptoms, obtained from multiple logistic regression analysis

GI symptom	Treatment	Odds ratio	*P* value	95% CI
Diarrhea	Tacrolimus	1.7	<0.0001	1.4–2.0
	Azathioprine	0.7	0.0002	0.6–0.9
Indigestion	Azathioprine	0.7	0.0051	0.6–0.9
	Prednisolone	1.3	0.0323	1.0–1.6
	Sirolimus	2.9	0.0420	1.0–8.1
Constipation	Tacrolimus	1.3	0.0033	1.1–1.6
	Prednisolone	1.3	0.0016	1.1–1.6
Abdominal pain	Sirolimus	2.2	0.0306	1.1–4.4
Any GI symptom	Azathioprine	0.7	0.0104	0.5–0.9

Odds ratios were adjusted for all variables included in the final models. For diarrhea, estimates were adjusted for country and time since transplantation. For indigestion, estimates were adjusted for country, age, donor, and time since transplantation. For constipation, estimates were adjusted for country, sex, and age. For abdominal pain, estimates were adjusted for country, sex, and age. For any GI symptom, estimates were adjusted for country, sex, and donor. Odds ratios and 95% CIs were calculated with the absence of the studied factor as the reference category in each case.

the mean scores found in renal transplant patients in this survey were higher than the scores found previously in the Swedish general population (*30*, *31*). These comparisons therefore suggest that the prevalence of GI symptoms in the Nordic renal transplant population is higher than in the general population.

Comparisons can also be made with the results of studies using other validated questionnaires. In the current survey, the prevalence of diarrhea among renal transplant patients (as defined as a GSRS score >1) was 53%, which is higher than previous measurements from the general population, which were in the range of 3.4–12.0% (*32*–*34*). Similarly, in the current survey population the prevalence of indigestion (a GSRS score >1) was 83%. This is higher than the prevalence of 15.5% measured in the Swedish general population (*35*). The prevalence of constipation was also higher in the renal transplant population than has been previously found in the general population. In our survey, 56% of patients had a GSRS score >1 for constipation. Swedish surveys of the general population have found the prevalence of constipation to be 8.0–14.3% (*36*, *37*), whereas a multinational study recorded a prevalence of 10.1% (*34*).

Close comparisons are available for abdominal pain as two studies have also employed the GSRS. Taking a GSRS rating ≥2, these studies found the prevalence of abdominal pain to be 24.9% and 41% in the general population of Denmark and Sweden, respectively (*20*, *38*). In our survey, the prevalence of a GSRS rating >2 was 28.8%, suggesting that the prevalence of abdominal pain is similar in the renal transplant population compared with the general population. A GSRS score for acid regurgitation ≥2 was found in 21.6% of the general population in Sweden (*20*), a prevalence similar to that found for reflux in the renal transplant population in our survey (GSRS >2 was 22.7%).

Renal transplant patients most commonly had impaired HRQoL compared with the general population for the SF-36 dimensions of general health, vitality, bodily pain, and physical functioning. This is consistent with a previous survey in the United States that found that the general health and physical functioning SF-36 dimensions were the most impaired in kidney transplanted patients (*7*). Similarly, in a Japanese study, although social and physical functioning dimensions improved after transplant surgery, patients still had impaired general health (*39*).

The results of our survey indicate that renal transplant patients most commonly had better HRQoL compared with the general population for the mental SF-36 dimensions of social functioning, role-emotional, and mental health. The survey carried out in the United States also found that fewer transplant patients had meaningfully impaired HRQoL in the social functioning, role-emotional and mental health dimensions than for the physical health dimensions (*7*).

HRQoL was most impaired for those renal transplant patients with severe GI symptoms, indicating that GI symptoms may be a major underlying reason for reduced HRQoL for these patients. The results found in this survey reflect those of other studies of GI symptoms in the general population that show that individuals with GI symptoms have impaired quality of life. Gastroesophageal reflux symptoms impair HRQoL in the general population (*20*, *40*) and affect work and leisure productivity (*41*). There is also strong evidence that people with moderate to severe irritable bowel syndrome who seek care for their symptoms have decreased HRQoL (*42*).

Tacrolimus, prednisolone, and sirolimus were associated with an increased likelihood of certain GI symptoms in the renal transplant population. The overall increase in the prevalence of GI symptoms in this population compared with the general population may therefore be due to side effects from these medications. Our study corroborates, in a large unselected patient population, the results of clinical trials and mechanistic studies which have previously identified an association between tacrolimus and GI symptoms (*43*–*46*). Clinical trials of mycophenolate mofetil have also reported GI side effects (*15*, *47*–*49*). In other studies, the percentage of patients taking mycophenolate mofetil who have experienced GI symptoms has been 27.3–49.1% (*16*, *18*). Although mycophenolate mofetil was not a significant predictor for any GI symptom in our survey, it is notable that the average dosage of this drug was less than the recommended starting dose of 2 g per day. It is possible that these patients had their mycophenolate mofetil dose reduced not by routine but because they had previously experienced GI symptoms. Coadministration of ciclosporin with mycophenolate mofetil is known to diminish the body's exposure to mycophenolate mofetil (*50*–*52*). Because most patients who took tacrolimus were also prescribed mycophenolate mofetil, it is possible that the increased association of GI side effects with tacrolimus may have been related to an increased exposure to mycophenolate mofetil compared with ciclosporin-treated patients, rather than a direct effect of tacrolimus itself.

This survey is the largest cross-sectional survey of HRQoL and GI symptoms in transplant patients yet performed, involving 4,232 patients from multiple centers in four European countries. The respondents were representative of the total Nordic postrenal transplant population and the survey used validated questionnaires with well-established norm values. The

use of validated questionnaires allowed for meaningful comparisons with other studies. Furthermore, the use of patient-reported rather than physician-reported outcomes is likely to have given a more realistic picture of the true symptoms and experiences of the patients, which is crucial for HRQoL assessment. Physicians have been shown to underestimate the presence and severity of GI symptoms in clinical trials (*53*, *54*), and the picture is likely to be the same in clinical practice. The response rate of the survey was high (70% overall), which means that we can be confident that the results represent the Nordic postrenal transplant population as a whole. However, there are several limitations that should be considered when interpreting the data presented. The survey itself did not include general population controls. We therefore compared the prevalence of GI symptoms and HRQoL scores with general population norms from other studies. Where other studies did not use the GSRS, variation in the definitions of GI symptoms used may have affected the accuracy of these comparisons. The two questionnaires had different recall periods, of one week (GSRS) and four weeks (SF-36). We did not collect information on comorbidity, kidney function, GI treatments, or other medications, which could have influenced our results. For example, diabetes has previously been shown to have an effect on HRQoL in renal transplant patients (*55*).

With the increasing success of renal grafts and decrease in patient mortality, optimizing HRQoL forms the main goal for long-term management of renal transplant patients. Although renal transplants improve all aspects of HRQoL, our survey indicates that renal transplant patients have a reduced HRQoL with respect to general health, vitality, physical functioning, and bodily pain compared with the general population. Furthermore, this may be related to the discomfort they experience due to GI symptoms. Identifying and managing GI symptoms in renal transplant patients should therefore be a priority.

Analysis of treatment effect in cross-sectional studies should be treated with caution because GI symptoms may influence treatment choice. However, our survey suggests that the choice of immunosuppressant has an impact on GI symptoms. In particular, tacrolimus was associated with an increased likelihood of diarrhea and sirolimus with abdominal pain. The design of immunosuppressive regimens should take this into account. However, care must be taken that dose reduction does not compromise graft survival. For example, in one study the risk of rejection increased by 4% for every week that the dosage of mycophenolate mofetil was reduced below the full dose (*56*). Similarly, in another study, the majority of patients taking mycophenolate mofetil had at least one dose change within their first posttransplant year and these patients had a significantly increased incidence of acute rejection ($P<0.001$) (*57*). Of the 507 patients who changed dosage, 21% did so because of GI symptoms. Changing to immunosuppressive treatments with less severe GI side effects may be preferable to radical dose reduction, which could compromise graft survival.

The negative effect of GI symptoms on HRQoL may also reduce compliance with immunosuppressive courses. This in turn increases the likelihood of graft rejection (*58*). GI symptoms tend to be underestimated by physicians in general (*53*), partly because patients often do not volunteer information about them (*59*). Careful questioning is required, and a patient-completed questionnaire asking about these symptoms could facilitate communication between patients and physicians. This could assist physicians in prescribing an immunosuppressive regimen that gives the patient the best possible quality of life, maximizing compliance, and minimizing the risk of acute graft rejection.

Our findings also have implications for research. In the future, validated questionnaires such as the GSRS should be used to give a more sensitive and standardized measurement of the GI symptoms in randomized controlled trials of immunosuppressive treatments. Currently, differentiating between GI symptoms caused by infection and those arising from drug toxicity is difficult, and yet it is important for informing treatment decisions (*52*). Future research addressing this issue would strengthen a physician's position in being able to choose the renal transplant immunosuppressive regimen that maximizes their patients' quality of life.

In conclusion, we report the largest international study yet to investigate HRQoL and GI symptoms in renal transplant patients. Nordic renal transplant recipients most commonly showed impaired HRQoL compared with the general population in the dimensions of general health, vitality, bodily pain, and physical functioning. In contrast, SF-36 scores in role-emotional, social functioning, and mental health dimensions were most frequently higher than in the general population. Our study corroborates the findings from studies of HRQoL performed in the United States and Japan, but also includes an analysis of the impact of GI symptoms on HRQoL, which has not previously been investigated. HRQoL was also reduced for every dimension when patients experienced troublesome GI symptoms, with HRQoL becoming more impaired the more severe the GI symptoms. The majority of renal transplant recipients experienced troublesome GI symptoms, giving a higher prevalence in this population than in the general population. Managing GI symptoms more effectively has the potential to improve HRQoL in renal transplant patients. By facilitating dose maintenance and improving compliance, this may lead to further improvements in graft survival rates.

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