

Gastrointestinal symptoms in kidney transplant recipients: what about silent sufferers?

Context—Transplantation improves health-related quality of life in patients with end-stage renal disease. However, primarily because of adverse effects of medication, among other gastrointestinal symptoms, health-related quality of life is not completely restored to normal. Although many patients have various gastrointestinal symptoms only a small proportion may be reported spontaneously.

Objective—To evaluate the prevalence of gastrointestinal symptoms in kidney transplant recipients, also the difference between spontaneously reported symptoms and symptoms elicited by specific questioning was assessed. The burden of these symptoms in daily life also was analyzed.

Design—A single-center, sequential, mixed method study to assess the difference between spontaneous patient reports of gastrointestinal symptoms and active screening by a questionnaire in kidney transplant patients.

Patients—In February 2008, patients received a questionnaire on gastrointestinal symptoms; notes in medical records were consulted for patients scoring less than 100. In June 2008, those patients received a second, extended questionnaire aimed to assess the burden of gastrointestinal symptoms in daily life.

Results—Ninety-two of 513 patients eventually proved to have gastrointestinal symptoms. Completed questionnaires were compared with notes in the patients' files of the past year. A total of 51 of these 92 patients appeared to have not mentioned their gastrointestinal symptoms during the outpatient clinic visits. Of these 51 patients, 37 reported a significant impact of gastrointestinal symptoms on daily life.

Conclusions—The silent sufferer exists. Specific questioning helps to improve communication concerning bothersome gastrointestinal symptoms. To assess the burden of these symptoms, a validated questionnaire should be developed.

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In patients with end-stage renal disease, transplantation markedly improves health-related quality of life. However, primarily because of adverse effects of medication (sexual dysfunction, headaches, changes in body shape, swelling of extremities, changes in facial shape, tremors, and easy bruisability), health-related quality of life is not completely restored to normal.¹ Furthermore, introduction of newer drugs into the immunosuppressive regimen may lead to other or additional adverse effects that interfere with daily life. Although not mentioned in the longitudinal life satisfaction analysis of Matas et al,¹ gastrointestinal adverse effects have recently been associated with both impaired health-related quality of life² and poor compliance,³ thus adversely affecting long-term graft survival.⁴

Although patients do exhibit various gastrointestinal symptoms, only a small proportion may be reported

spontaneously. After specific questioning, Ekberg et al⁵ found the following prevalence of troublesome gastrointestinal symptoms in a cohort of 4232 kidney transplant patients: 83% indigestion, 69% abdominal pain, 58% constipation, 53% diarrhea, 47% reflux, and 92% for any gastrointestinal symptom. Clinicians treating kidney transplant patients, however, estimated the prevalence of these symptoms at less than 10%. Ekberg et al² reported a strong association between tacrolimus and sirolimus and gastrointestinal symptoms.

Mycophenolate mofetil adjunctive therapy has been associated with a 32% to 75% incidence of diarrhea for patients after kidney transplantation,⁶ which may be persistent in 50% of cases after 1 year.⁷ Therefore, a prevalence of bothersome gastrointestinal symptoms of 20% to 50% could be anticipated in the cohort of kidney patients at the University Medical Centre Groningen,

in accordance with a 47% prevalence of diarrhea for maintenance patients on cyclosporine plus mycophenolate mofetil.⁸

If patients do not effectively communicate adverse effects, clinicians may not have the information to adapt treatment and support patient compliance appropriately. This is especially the case when transplant patients are reluctant to bother the transplant team with nuisance symptoms. Therefore, specific questioning may help patients to come forward with bothersome gastrointestinal symptoms that can be improved with various strategies.⁹⁻¹¹ Thus, health-related quality of life may be improved along with compliance and possibly graft survival.

The aim of this survey was to evaluate the prevalence of gastrointestinal symptoms in kidney transplant recipients, relate the reporting of gastrointestinal symptoms to demographics, to assess the difference between spontaneous reports of gastrointestinal symptoms and symptoms elicited on specific questioning and to determine the burden of those symptoms in daily life.

Design/Methods

Design

This single-center, sequential, mixed method study was done to assess the difference between patients' spontaneous reports of gastrointestinal symptoms and symptoms revealed by active screening (via questionnaire).

Sample

A sample of convenience was pulled from our kidney transplantation population. We studied 513 patients receiving a donor kidney in the period from January 1998 to January 2005 who were on a stable immunosuppressive regimen.

Instruments

In the first stage of the study, specific questioning was done by means of the Gastrointestinal Quality of Life Index (GIQLI), a 36-item questionnaire designed to assess the effects of gastrointestinal symptoms and disease on daily life. The GIQLI has 5 subscales: gastrointestinal symptoms (addressing all kinds of inconvenience and pain in the abdomen and bowel, such as fullness, gurgling noises, regurgitation, diarrhea, nausea, heartburn), emotional status, physical function, social function, and an item addressing stress of medical treatment. For each question, the scores range from 0 to 4. The higher the scores, the better the patient is feeling.

The GIQLI has been validated in the kidney transplant population in a cross-sectional study conducted at 5 clinical centers in 4 countries and was reported to possess good validity.⁶ Reliability of the gastrointestinal symptoms subscale was 0.90, and the scale showed satisfactory known groups validity. The

total scores of the GIQLI range from 0 to 144. Higher scores represent better health-related quality of life.

In the second stage, the aim was to assess the prevalence of gastrointestinal symptoms as well as the burden (degree of suffering) caused by those symptoms. For this purpose, items 1 through 8 and 17 through 27 (which concern gastrointestinal symptoms) of the GIQLI were asked again and were extended with a question about how the experienced severity of the symptom bothered the patient, measured on a 5-point tediousness scale where 0 = none, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe.

The score on the severity/prevalence of the gastrointestinal symptom was mirrored, so a high score reflected high severity/prevalence of the symptom. The severity/prevalence score was multiplied with the tediousness score to arrive at an impact score.

Reliability of the gastrointestinal subscale in the second stage ($n = 69$) was 0.81, and the test-retest reliability was 0.51 ($n = 69$, $P < .001$), an acceptable score given that both tests were administered 4 months apart and symptoms from a number of patients were subject to change during that period. The tediousness scale had a reliability of 0.88. The gastrointestinal subscale in the second stage correlated strongly (Pearson correlation 0.82, $P < .001$) with the tediousness scale.

Scores were classified as follows: score < 76 , mild; score > 76 , moderate; score > 114 , severe suffering. To arrive at a score of 76, for example, all 19 items were scored as moderate on severity and tediousness, giving an impact score of $2 \times 2 = 4$. To arrive at a score of 114, for example, all items were scored as moderate on severity and as severe on tediousness (or the other way round), giving an impact score of $2 \times 3 = 6$.

For the third stage of the study, the information from these follow-up forms was calculated and was discussed with the patient in person during a regular visit to the hospital or by phone.

The patient was also asked:

1. "Do you expect there is any cure for the gastrointestinal symptoms?"
2. "If not, why not?"
3. "If so, why didn't you ask us?"
4. "When you compare your present health situation to the situation before you were transplanted, is it now better, worse, or equal?"

The answers to these questions were not analyzed in detail, but they were used in the conversations with the patients in the outpatient clinic, when the outcome of the forms and the likelihood of changing the therapy were discussed.

Procedure

The study consisted of 2 quantitatively oriented stages (GIQLI and extended GIQLI) and 1 more qualitatively oriented stage (semiquantitative patient interview).

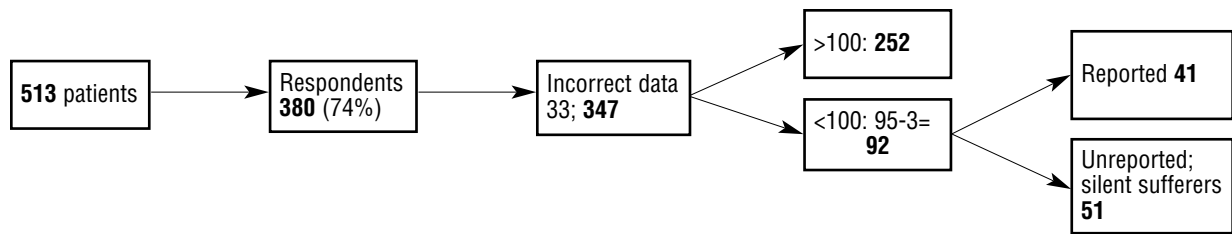


Figure 1 Diagram of response rate of patients completing the Gastrointestinal Quality of Life Index.

The completed GIQLI questionnaires were scanned and the scores were processed automatically. In patients with a score less than 100, the GIQLI scores were compared with the gastrointestinal notes in the patients' files during the past year. The outpatient clinic files were subjected to textual assessment.

This point (<100) was chosen on the basis of the study of Chan et al,¹⁰ where in 101 patients with gastrointestinal complaints, the mean (SD) score was 90.4 (20.7); in 177 patients without gastrointestinal complaints, the mean score was 122.7 (14.6). When patients had reported their gastrointestinal symptoms, we called them reporters, patients who did not mention gastrointestinal complaints are classified as non-reporters, "silent sufferers."

In June 2008, a second questionnaire as described earlier was sent to the 92 patients scoring less than 100 on the GIQLI forms. A total of 74 patients (80%) returned the form, of which 4 contained incorrect data, so 70 (76%) were eligible for analysis.

After returning the second forms, the patients were seen in the outpatient clinic or were contacted by telephone. They were offered (depending on the symptoms) the chance to switch the immunosuppressive medication, to add or switch gastrointestinal medication, or to consult a gastroenterologist. In the time between the first and the second form, 2 patients went back to dialysis.

Analysis

Significance was assessed by using nonparametric χ^2 tests (and $\alpha = .05$). The subscales were not scored separately; they were used to extract the gastrointestinal symptoms.

Results

Population of Patients

In the beginning of February 2008, 513 recipients of a renal allograft received a GIQLI questionnaire. All these patients had received a donor kidney in the period from January 1998 to January 2005. In total 380 patients (74%) returned the form. Not all questionnaires were completed correctly, 33 forms contained incorrect data, so eventually 347 were accepted for further analysis.

In 95 (27%) patients we found a score less than 100. Three of these patients did not visit the outpatient clinic for 3 years, so they were excluded from the study. After the completed GIQLI was compared with the notes in the patients' files, it proved to be that 41 (45%) mentioned their symptoms, but 51 (55%, the silent sufferers), did not (Figure 1).

Demographics and Patient Characteristics

In this population, 69 patients were 50 years old or more, and 61% were nonreporters, against only 39% of the group less than 50 years old (Pearson $\chi^2 = 3.30$, $P = .07$). Of the 48 male respondents, 58% were non-reporters, compared with 52% of the 44 female respondents ($P = .28$). Race and the presence of diabetes mellitus did not play a role in being a nonreporter (Table 1).

Immunosuppressive Treatment

Almost all patients (99%) received corticosteroids. A majority of 72% received an immunosuppressive regimen containing mycophenolate mofetil. Forty-five patients received immunosuppressive medication including calcineurine inhibitors: 24 (26%) containing cyclosporin A, 21 (23%) containing tacrolimus. A minority of patients (20%) received an immunosuppressive scheme that contained azathioprine (10%), enteric-coated mycophenolate mofetil (7%), or sirolimus (2%) (Figure 2).

Assessment of the Burden of Gastrointestinal Symptoms

In 62 of the 70 responding patients with no incorrect data (89%), we found a score from 0 to 76 (36 of them were nonreporters), indicating a mild burden of suffering due to gastrointestinal symptoms. Only in 8 patients (11%, 1 nonreporter) was a score from 76 to 123 found, indicating moderate suffering, none scored more than 124 (Figure 3).

In the qualitative assessment, the majority of the patients (77%) either accepted the discomfort or the symptoms were in the meantime strongly improved. Others decided, after the gastrointestinal symptoms had been discussed with the nephrologists in the outpatient clinic, that they had no wish to follow up. In all

Table 1 Relationship between demographic characteristics and reporting or not reporting

Characteristic	No. (%) of patients		Total	Pearson χ^2	P
	Reporters	Nonreporters			
Age, y				3.30	.07
≥ 50	27 (39)	42 (61)	69		
< 50	14 (61)	9 (39)	23		
Sex				0.34	.28
Male	20 (42)	28 (58)	48		
Female	21 (48)	23 (52)	44		
Diabetes mellitus				0.03	.86
Yes	9 (43)	12 (57)	21		
No	32 (45)	39 (55)	71		
Race				1.17	.28
White	37 (47)	42 (53)	79		
Not white	4 (31)	9 (69)	13		

these cases, the patients had no wish to go to the gastroenterologist for further analysis.

In only 10 patients (14%) was either the immunosuppressive regimen changed or the gastrointestinal medication added or switched. Patients who report gastrointestinal symptoms more often discuss the symptoms, and among the nonreporters, the gastrointestinal symptoms are more often improved or accepted by the patients (Table 2).

Discussion

From their Scandinavian survey, Ekberg et al⁵ reported that gastrointestinal symptoms tend to be underestimated and that improving communication between clinicians and patients could lead to more informed management. The aim of our study was to investigate if the results reported by Ekberg et al are also valid for a Dutch kidney transplantation cohort.

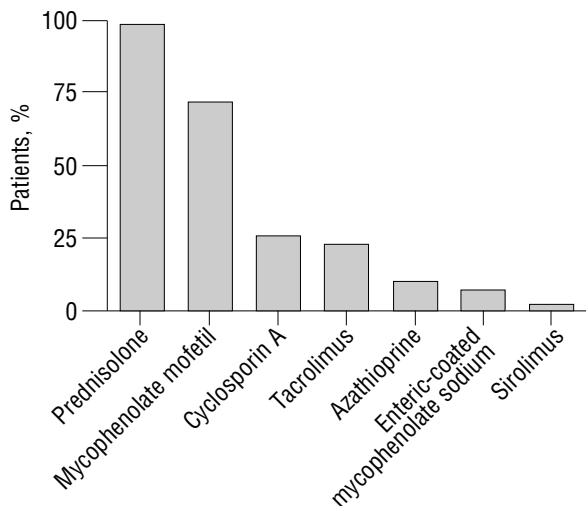


Figure 2 Immunosuppressive medication used by 92 patients with gastrointestinal signs and symptoms (score < 100).

In our study we used the GIQLI, a validated questionnaire about gastrointestinal quality of life. The response rate in this study (74%) was high (and so we had a representative overview of the amount of gastrointestinal symptoms that patients had). However, the general feeling was that the results from the GIQLI did not correspond to the burden that patients with gastrointestinal symptoms experienced. Results from the GIQLI suggested that the patients had gastrointestinal symptoms, but the results did not inform about the effects of this suffering on patients' daily life. Therefore we made a questionnaire that gave us more accurate access to the real burden of the gastrointestinal symptoms patients had.

Indeed, the results from this second questionnaire showed us that only 38 patients reported a significant burden of gastrointestinal symptoms affecting daily life, of a total of 92 patients who came out as sufferers according to the results from the GIQLI.

One of the intentions of this study was to construct a profile of silent sufferers. Although most of the nonreporting patients were male, 50 years old or more, and had received a transplant approximately 5 years ago, the differences in these factors between reporters and nonreporters were not statistically significant. Also we found no significant difference in age, sex, ethnic origin, or the prevalence of diabetes between reporters and nonreporters in this study. Therefore, we cannot construct a "silent sufferer profile" based on the results from our study.

In the second questionnaire, the patients were asked why they did not report the symptoms. Most of the silent sufferers were reluctant to report their symptoms because they were unwillingly to undergo further evaluation. They were tired of medical examinations and chose to accept the discomfort. The fact that among the nonreporters, the gastrointestinal symptoms are more often improved or accepted by the patients

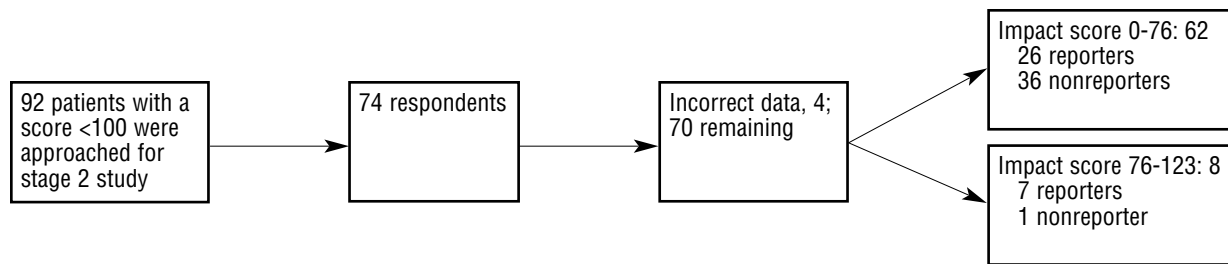


Figure 3 Response rate and scores for burden of gastrointestinal signs and symptoms.

could also indicate that the gastrointestinal symptoms are less severe than among the group reporting those symptoms.

Another reason for not reporting the discomfort was because patients were afraid that the physician would change their current immunosuppressive regimen and that change might affect graft function. These fears are most likely a topic for many patients, not to mention the ways in which they cope with complaints and become silent sufferers.

The question is, How can we better identify these silent sufferers? A strategy that could help to improve patients' quality of life by identifying gastrointestinal symptoms could be use of a questionnaire. When using such a list, at every visit of the patient in the outpatient clinic, the same questions about gastrointestinal symptoms will be addressed. By asking the patient the same questions routinely at every visit, patients might be better prepared for their visits and their visits would be more efficient. Another strategy could be setting up special nursing consulting hours. Nurses tend to be more approachable than physicians and probably can spend more time with patients to discuss problems.

A limitation of this study is that the second questionnaire is a nonvalidated questionnaire. Another item is our study population: transplant recipients at our center live mainly in the countryside. A number of them are people working in the agrarian sector, and they are known for working physically and being

noncomplainers when it comes to pain or inconvenience. These factors may have biased the outcome, because the population studied might differ from the general Dutch population.

We confirmed the result reported by Ekberg et al⁵ on the existence of silent sufferers in a Dutch kidney transplant population. In this survey, 92 kidney transplant patients reported troublesome gastrointestinal symptoms on the GIQLI form. In 55% of these cases, complaints had not been reported in the patient visits during the past year.

We also corroborated that better communication increases clarity; specific questioning helps patients to come forward with bothersome symptoms. It can be said, silent sufferers exist. Therefore, we agree on this subject with Ekberg et al²: careful questioning is essential. However, in the end, either a gastrointestinal medication was added or switched or the immunosuppressive regimen was altered in only 10 patients (11%). Thus, the burden of the symptoms does not as a whole correspond to the prevalence of the symptoms.

If only the GIQLI is used, it is difficult to assess the burden of suffering. Therefore, if identifying silent sufferers is desirable, this new questionnaire, in which both prevalence and burden of gastrointestinal symptoms are being assessed, must be validated. All the questions in the GIQLI should be extended with the question: "In what way is this bothering you?" followed by the following responses (one should be circled): none, mild, moderate, severe, very severe.

Table 2 Results from second questionnaire related to reporting behavior

Result	No. (%) of patients			Pearson χ^2	P
	Reporters	Nonreporters	Total		
Back to dialysis	2 (100)	0 (0)	2		
No wish to follow up, reasons				2.33	.06
Gastrointestinal signs and symptoms improved or accepted	18 (41)	26 (59)	44		
Gastrointestinal signs and symptoms discussed	9 (64)	5 (36)	14		
Treatment				2.86	.091
Switch immunosuppressive regimen	4 (57)	3 (43)	7		
Switch or add supplementary gastrointestinal medication	0 (0)	3 (100)	3		

Conclusions

For the well-being of our patients, improvement in communication between physicians and patients is essential, and communication can probably be enhanced further by initiating nursing consulting hours. Silent sufferers with an objective burden of their complaints in daily life exist. To identify these patients, the GIQLI should be extended with an additional questionnaire specifically addressing the burden caused by gastrointestinal symptoms. This specific questionnaire is essential to understand fully the effects of medication-related adverse effects and to offer patients the most appropriate treatment.

Financial Disclosures

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