

Distress associated with adverse effects of immunosuppressive medication in kidney transplant recipients

Context—For kidney transplant patients, a lifelong intake of medication is mandatory. Health care workers' prioritization of adverse effects often differs from that of their patients, although patients' experience of adverse effects of medication can trigger nonadherence. Understanding how patients experience symptoms is therefore important.

Objective—To present a new method to be used in research to evaluate symptom experience related to adverse effects in adult kidney transplant recipients on maintenance immunosuppressive therapy.

Design—Cross-sectional secondary data analysis.

Patients and Setting—Three hundred fifty-six adult kidney transplant recipients from 2 Swiss transplant outpatient clinics.

Main Outcome Measures—Symptom experience was measured with the Modified Transplant Symptom Occurrence and Symptom Distress Scale. For each item, rdit scores were calculated. A coordinate system with occurrence and distress ratings of each symptom classified symptoms into 4 quadrants: symptoms could have high occurrence/high distress, low occurrence/high distress, high occurrence/low distress, and low occurrence/low distress symptoms. Items farther from the origin represented more extreme profiles.

Results—The proposed method arranges symptoms clearly in sequence of their importance. In our study, fatigue and joint and back pain were the most frequent and distressing symptoms. Symptom profiles for men and women differed: for men impotence and anxiety were key whereas for women listlessness and changed appearance seemed to play important roles.

Conclusions—The 2-dimensional diagram of symptom profiles enables researchers and clinicians to evaluate the impact of symptoms associated with immunosuppressive medications. (*Progress in Transplantation*. 2010;20:40-46)

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Kidney transplantation requires a lifelong intake of medication to prevent the immune system from rejecting the received kidney. Unavoidably, patients experience symptoms related to adverse effects. Symptom experience consists of 2 distinct but interrelated aspects. The first is occurrence, the cognitive component of symptom experience. The second, emotional aspect refers to the distress a symptom engenders.¹ The most common symptoms are not necessarily the most distressing,² and the most distressing symptoms are not necessarily the most life-threatening.³ Often, health care workers' prioritization of adverse effects differs from that of their patients, namely, health care workers tend to focus on life-threatening symptoms, whereas patients often attach high significance to other symptoms. The degree to which patients experience symptoms and find them distressing is highly subjective and

is influenced by personal and socioenvironmental factors including the patient's sex, depression, previous illness experiences, and socioeconomic status.³⁻⁵ Women, for example, score higher on symptom experience and report different symptoms than men report.⁴

Studying symptom experience from a patient's perspective is important: patients may conclude that treatment is making them sick rather than keeping them in healthy condition, resulting in nonadherence to the prescribed medication regimen.⁶ The aim of this study is therefore to assess symptom experience in adult kidney transplant recipients on maintenance immunosuppressive therapy and to compare and classify different symptoms according to their occurrence and distress ratings.

Symptom experience consists of 2 parallel and interrelated parts: symptom occurrence (frequency,

severity and duration) and symptom distress, the subjectively perceived burden of a symptom.

We now propose a descriptive method to picture symptom profiles, build rank orders, and take the 2-dimensional interrelatedness of symptom occurrence and symptom distress into consideration. Because various studies have reported differences in symptom profiles between men and women, this exploration of symptoms is sex specific.

Materials and Methods

Design

This cross-sectional study is part of a larger research project aimed at determining prevalence and correlates of nonadherence with immunosuppressive regimes after kidney transplantation.⁷

Sample and Setting

This study's convenience sample included patients on immunosuppressive medication, at least 18 years old, more than 1 year after kidney transplantation, able to read and write German or French, able to independently manage their medication regimens, being followed up at 1 of the 2 participating transplant outpatient clinics, and mentally capable of adequately responding to the researcher's questions and to fill out the questionnaires. Patients not able to read the questionnaires because of poor vision or mental disorders were excluded.

Variables and Measurement

Symptom experience frequently associated with adverse effects of immunosuppressive medications was measured with the 45-item version of the Modified Transplant Symptom Occurrence and Symptom Distress Scale (MTSOSDS).⁸⁻¹⁰ This self-report instrument consists of 45 items representing symptoms frequently associated with cyclosporine A, tacrolimus, azathioprine, corticosteroids, and mycophenolate mofetil (Cellcept). The instrument measures symptom occurrence on a 5-point scale ranging from 0 (never occurring) to 4 (always occurring), and symptom distress on a visually distinct 5-point scale ranging from 1 (not at all distressing) to 5 (extremely distressing) within the last month. Distress scores were deleted if symptom occurrence was indicated as not present (=0) (anticipatory distress). Female/male versions differ in item 9: Painful/excessive menstruation and Impotence. For the Swiss population the adapted instrument was translated into German following a standard translation protocol.¹¹

Validity of the MTSOSDS has previously been evaluated.¹² Unrotated principal component analysis on the occurrence items of this sample showed that the shared variance among the items was only 16%, indicating that the items did not share a lot of information

and that symptom occurrence was not a unified construct. Consequently, we considered each item as a separate variable and did no further reliability testing.

Data Collection

Data collection occurred between June 2001 and January 2004. Patients were approached at the outpatient clinics by masters-prepared nurses during the patients' regular yearly follow-up visits. After patients had provided informed consent, demographic variables were collected. Patients received the MTSOSDS to be completed at home. They were asked to return these in the provided prestamped, preaddressed envelope.

Upon their delivery, the questionnaires were checked for completeness. In cases of missing data, patients were telephoned. Clinical data (eg, immunosuppression dose) were extracted from participants' medical files.

Data Analysis

Data analysis was done using SPSS 11.0 (SPSS Inc, Chicago, Illinois). Demographic and clinical variables were expressed as means and standard deviations, or as percentages, depending on the distribution. Symptom distress data were checked for anticipatory scores; anticipatory distress scores were deleted.

We used ridit analysis, a method of analysis for ordinal data, to rank symptom occurrence and symptom distress items.¹³ Ridit analysis compares the frequency distribution of a variable with the frequency distribution of that variable in a reference group. The resulting score, or ridit, ranges from minimum 0 to maximum 1 and represents the probability that a randomly selected subject of the test group would score higher on the variable than a randomly selected subject from the reference group. A ridit of 0.5 represents equal probability whereas ridits greater than 0.5 stand for a higher probability. We chose the frequency distribution of all items over all patients as the reference distribution, and we conducted separate analyses for men and women.

We plotted all items' ridit scores in a coordinate system in which the x-axis represented the ridit on symptom occurrence and the y-axis represented the ridit on symptom distress (see Figure). The 4 quadrants represented the different profiles of items: low occurrence/low distress, high occurrence/low distress, low occurrence/high distress and high occurrence/high distress. The origin of the ridit plot is situated at 0.5, providing a cutoff. Items farther from the origin represent more extreme profiles. The degree of extremeness was quantified by calculating the length of each item's vector from the origin (VL), by using the formula: $VL_{item_i} = \sqrt{(SO_{item_i} - 0.5)^2 + (SD_{item_i} - 0.5)^2}$, where SO is symptom occurrence and SD is symptom

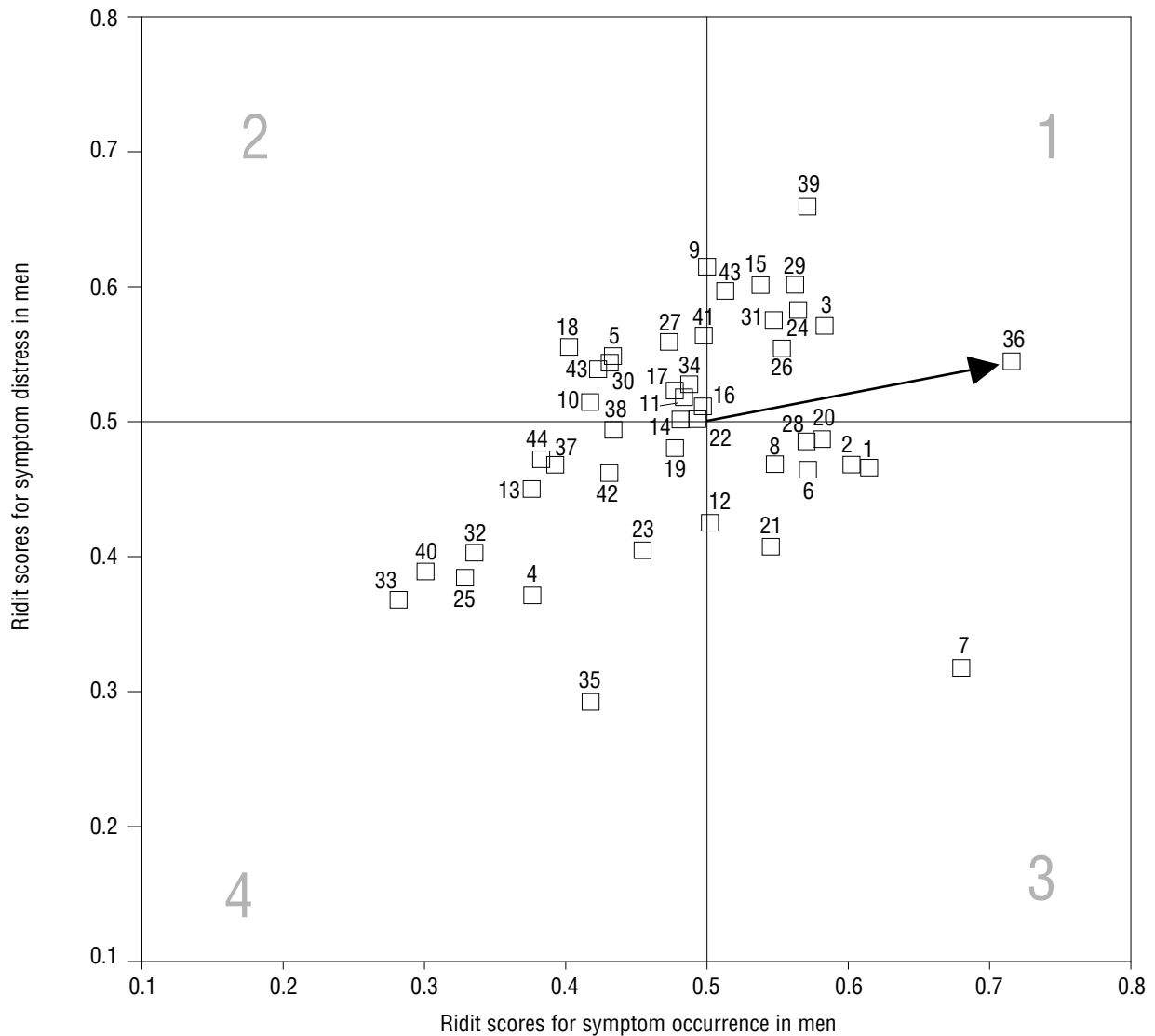


Figure Scatterplot of ridit scores for symptom occurrence and symptom distress for men (reference group: all patients over all items) for illustration of the method. Arrow shows the length of symptom 36's vector from the origin.

distress. Large VLs represented large differences from the average item, indicating a more extreme symptom profile. An item's ranking within each quadrant was determined by VL.

Differences between the sexes were assessed by the following criteria: when 2 items scored in the same quadrant, they were considered similar. For items found in different quadrants, we calculated distances between corresponding items of men and women.

To determine differences between groups we defined items within a distance of 0.05 units as similar, even when they were found in different fields (also because in these cases these items did not represent extreme symptoms because they lay very near an axis). VLs of the remaining items were compared between men and women.

Results

Characteristics of Patients

A total of 413 eligible patients were asked to participate in the study; 57 (13.8%) opted not to participate. Table 1 gives an overview of the sample's demographic and clinical characteristics (N=356). A minority of patients indicated anticipatory distress scores. Seventy-seven distress scores were deleted (0.89% of 8656 items that were scored as not occurring). Immunosuppressive regimens consisted of cyclosporine A, tacrolimus, azathioprine, sirolimus, mycophenolate mofetil, and corticosteroids in either monotherapy or combination therapy.

Ranking of the Symptoms

An item's ranking within each quadrant was determined by VL, with a large VL representing a more

Table 1 Demographic and clinical characteristics of 356 kidney transplant recipients

| Characteristic | Total | Men | Women | P |
|--|---------------|---------------|---------------|-----|
| No. (%) of recipients | 356 (100) | 207 (59) | 149 (41) | |
| Age, mean (SD), y | 52.92 (13.53) | 51.84 (13.62) | 54.40 (13.31) | .08 |
| No. of medications other than immunosuppressive medications, mean (SD) | 4.23 (0.13) | 4.24 (0.13) | 4.22 (0.12) | .08 |
| Cyclosporine, No. of recipients receiving | 228 | 130 | 98 | .60 |
| Daily dose, mean (SD), mg/kg | 2.78 (1.06) | 2.74 (0.94) | 2.82 (1.21) | |
| Mean daily dose, minimum/maximum, mg/kg | 0.72/8.52 | 1.17/6.06 | 0.72/8.52 | |
| Mycophenolate mofetil (Cellcept), No. of recipients receiving | 170 | 107 | 63 | .62 |
| Daily dose, mean (SD), g/m ² | 21.86 (9.74) | 21.62 (8.96) | 22.25 (10.92) | |
| Mean daily dose, minimum/maximum, g/m ² | 3.85/62.76 | 4.47/44.58 | 3.85/62.76 | |
| Azathioprine, No. of recipients receiving | 115 | 66 | 49 | .34 |
| Daily dose, mean (SD), mg/kg | 1.38 (0.53) | 1.42 (0.54) | 1.32 (0.53) | |
| Mean daily dose, minimum/maximum, mg/kg | 0.28/3.16 | 0.28/3.16 | 0.46/2.73 | |
| Corticosteroids, No. of recipients receiving | 93 | 53 | 40 | .30 |
| Daily dose, mean (SD), mg/kg | 0.10 (0.04) | 0.10 (0.04) | 0.10 (0.03) | |
| Mean daily dose, minimum/maximum, mg/kg | 0.03/0.28 | 0.03/0.28 | 0.05/0.18 | |
| Tacrolimus, No. of recipients receiving | 64 | 38 | 26 | .83 |
| Daily dose, mean (SD), mg/kg | 0.06 (0.03) | 0.06 (0.03) | 0.06 (0.03) | |
| Mean daily dose, minimum/maximum, mg/kg | 0.01/0.14 | 0.02/0.14 | 0.01/0.13 | |
| Sirolimus, No. of recipients receiving | 25 | 18 | 7 | .12 |
| Daily dose, mean (SD), mg/kg | 0.06 (0.05) | 0.05 (0.04) | 0.08 (0.07) | |
| Mean daily dose, minimum/maximum, mg/kg | 0.01/0.22 | 0.01/0.14 | 0.01/0.22 | |

extreme symptom (high or low). The sequences are presented in Tables 2 and 3.

Table 2 shows results of the ridit calculations for males. Ten items were situated in the field "often and distressing," 12 items in the field "not often but distressing," 9 items in the field "often but not distressing," and 14 items in the field "not often and not distressing." Tiredness, joint pain, and sleeping disturbances were the 3 most distressing and most common symptoms. The top 3 least frequently occurring but still distressing symptoms for men were anxiety, mouth infections, and swollen gums.

Table 3 shows the results of the ridit calculations for women. Women scored 17 items within the field "often and distressing," 8 items within the field "not often but distressing," 8 items within the field "often but not distressing," and 12 items within the field "not often and not distressing." The 3 most distressing and most common symptoms for women were tiredness, joint pain, and brittle skin, and the 3 most distressing but infrequently occurring items were painful/excessive menstruation, rash, and mouth infections.

Differences Between Sexes

The number of items in quadrant 1 (frequent and distressing) varied between sexes: women scored 17 items, whereas men scored 10 items as frequent and distressing. A total of 27 items were scored within the same fields for men and women. The following 18

items were scored within different fields: spots on face, listlessness, swollen gums, swollen ankles, stomach complaints, anxiety, changed appearance, headaches, changed facial features, increased light sensitivity, bruises and abdominal pain. Also, impotence/excessive painful menstruation, which represents a sex-related item, was scored in different fields. After vector lengths and distances between corresponding items were calculated for men and women, the following items remain for special consideration:

- Changed appearance was rated as occurring often and being distressing for women, but rated as occurring not often and being not distressing for men.
- Listlessness was rated as occurring often for both sexes but as being distressing for women only.
- Anxiety was rated as occurring not often for both sexes but rated as being distressing for men only.
- Impotence was rated as occurring often and as being distressing for men.
- Painful excessive menstruation was rated as occurring not often but rated as being distressing for women.

Discussion

We evaluated symptom experience related to adverse effects of immunosuppressive medication in 356 kidney transplant patients by using a 2-dimensional

Table 2 Ranking of men's symptoms by quadrant (reference group: all patients over all items)^a

| Men | | Symptom occurrence | | | | | |
|------------------|----------------------------|---------------------------|-------------------------------|-----------------------|--|-------------------------------------|-------|
| | | Not often | | Often | | | |
| | | Not often but distressing | | Often and distressing | | | |
| Symptom distress | Distressing | 18 | Anxiety | 0.112 | 36 | Tiredness | 0.220 |
| | | 45 | Mouth infections | 0.086 | 39 | Joint pain | 0.175 |
| | | 10 | Swollen gums | 0.083 | 29 | Sleeping disturbances | 0.118 |
| | | 5 | Depression | 0.082 | 9 | Impotence | 0.115 |
| | | 30 | Increased light sensitivity | 0.082 | 3 | Blurred vision | 0.110 |
| | | 41 | Rash | 0.065 | 15 | Back pain | 0.108 |
| | | 27 | Warts | 0.065 | 24 | Brittle skin | 0.104 |
| | | 17 | Stomach complaints | 0.032 | 43 | Muscle cramps | 0.095 |
| | | 34 | Trembling hands | 0.028 | 31 | Muscle weakness | 0.090 |
| | | 11 | Swollen ankles | 0.024 | 26 | Difficulties in concentration | 0.076 |
| | 16 | Hair loss | 0.010 | | | | |
| | 22 | Headaches | 0.007 | | | | |
| | Not distressing | | Not often and not distressing | | Often but not distressing | | |
| | | 33 | Hallucinations | 0.253 | 7 | Feeling of warmth in hands and feet | 0.258 |
| | | 40 | Painful urination | 0.226 | 1 | Spots on the face | 0.120 |
| | | 35 | Decreased appetite | 0.223 | 2 | Listlessness | 0.108 |
| | | 25 | Vomiting | 0.207 | 21 | Cough | 0.106 |
| | | 32 | Changed sense of taste | 0.109 | 20 | Mood swings | 0.084 |
| | | 4 | Fever | 0.176 | 6 | Extensive appetite | 0.080 |
| | | 13 | Moon face | 0.135 | 12 | Diarrhea | 0.076 |
| 44 | | Nightmares | 0.121 | 28 | Increased hair growth on face and body | 0.073 | |
| 37 | | Bruises | 0.112 | 8 | Decreased interest in sex | 0.058 | |
| 23 | Changed facial features | 0.107 | | | | | |
| 42 | Abdominal pain | 0.081 | | | | | |
| 38 | Tingling in hands and feet | 0.064 | | | | | |
| 19 | Changed appearance | 0.029 | | | | | |
| 14 | Feeling stressed | 0.020 | | | | | |

^a Number to the left of symptom is the symptom's number in the instrument and number to the right of the symptom is the length of that symptom's vector from the origin.

symptom experience chart representing both the symptom occurrence and symptom distress dimensions. This 2-dimensional representation allowed evaluation of symptoms from a patient's perspective. A listing that distinguishes distressing symptoms that occur often from those that are less distressing and occur only rarely is valuable information for both researchers and clinical practitioners.

The 2-dimensional method used in this study provides valuable information about the impact of each symptom in relation to other symptoms frequently associated with immunosuppressive agents. Items at greater distances from the origin represent a more extreme profile. All symptoms listed in quadrant 1 (Tables 2 and 3), especially the ones far from the center (large VL), occur often and cause considerable distress. The evaluation of adverse effects of medications is an important task for transplant clinicians. The current study describes symptom experience associated with these adverse effects along the 2 most relevant dimensions, namely, symptom occurrence and symptom distress, yet it also combines these 2 dimensions. This arrangement allows transplant clinicians to identify which symptoms appear in the different quadrants and can

thus provide more balanced information for patients and their families about what to expect in view of symptom experience in the posttransplant course. The high-occurrence dimensions show what a transplant patient can expect most frequently to experience after transplant. Yet, attention should be given most to symptoms with high distress (both in high and low occurrence sections) as such symptoms are linked to poor quality of life and nonadherence with immunosuppressive regimen.^{2,7} Kidney transplant recipients should therefore also be screened for and informed about those symptoms in quadrant 2. Those symptoms that are neither frequently occurring nor distressing are interesting from a psychometric point of view. Leaving these items out of the scale may diminish the burden for patients of filling out a long questionnaire.

Similar to previous studies, results of which indicated limited shared variance between the concepts of symptom occurrence and symptom distress, we found that the most frequently occurring symptoms are not necessarily the most distressing ones.^{2,12,14} Unlike previous research, the highest ranking items on both dimensions were not necessarily the highest ranking items in a previous study.¹⁵ Within the symptoms that

Table 3 Ranking of women's symptoms by quadrant (reference group: all patients over all items)^a

| Women | | Symptom occurrence | | | | | |
|------------------|-----------------|-------------------------------|--------------------------------|-----------------------------|-------|--|-------|
| | | Not often | | Often | | | |
| | | Not often but distressing | | Often and distressing | | | |
| Symptom distress | Distressing | 9 | Painful/excessive menstruation | 0.166 | 36 | Tiredness | 0.240 |
| | | 41 | Rash | 0.104 | 39 | Joint pain | 0.208 |
| | | 45 | Mouth infections | 0.092 | 24 | Brittle skin | 0.201 |
| | | 42 | Abdominal pain | 0.063 | 3 | Blurred vision | 0.181 |
| | | 5 | Depression | 0.056 | 15 | Back pain | 0.173 |
| | | 27 | Warts | 0.044 | 31 | Muscle weakness | 0.159 |
| | | 34 | Trembling hands | 0.024 | 29 | Sleeping disturbances | 0.138 |
| | | 38 | Tingling in hands and feet | 0.018 | 2 | Listlessness | 0.132 |
| | | | | | 20 | Mood swings | 0.123 |
| | | | | | 26 | Difficulties in concentration | 0.115 |
| | | | 43 | Muscle cramps | 0.105 | | |
| | | | 19 | Changed appearance | 0.096 | | |
| | | | 17 | Stomach complaints | 0.080 | | |
| | | | 11 | Swollen ankles | 0.062 | | |
| | | | 1 | Spots on the face | 0.032 | | |
| | | | 30 | Increased light sensitivity | 0.028 | | |
| | | | 14 | Feeling stressed | 0.008 | | |
| Symptom distress | Not distressing | Not often and not distressing | | Often but not distressing | | | |
| | | 33 | Hallucinations | 0.401 | 7 | Feeling of warmth in hands and feet | 0.283 |
| | | 35 | Decreased appetite | 0.222 | 23 | Changed facial features | 0.138 |
| | | 4 | Fever | 0.191 | 8 | Decreased interest in sex | 0.135 |
| | | 40 | Painful urination | 0.182 | 21 | Cough | 0.128 |
| | | 32 | Changed sense of taste | 0.150 | 28 | Increased hair growth on face and body | 0.108 |
| | | 25 | Vomiting | 0.141 | 37 | Bruises | 0.094 |
| | | 10 | Swollen gums | 0.133 | 22 | Headaches | 0.082 |
| | | 13 | Moon face | 0.095 | 6 | Extensive appetite | 0.073 |
| | | 44 | Nightmares | 0.034 | | | |
| 12 | Diarrhea | 0.033 | | | | | |
| 16 | Hair loss | 0.028 | | | | | |
| 18 | Anxiety | 0.001 | | | | | |

^a Number to the left of symptom is the symptom's number in the instrument and number to the right of the symptom is the length of that symptom's vector from the origin.

have been addressed by the MTSOSDS, the highest ranking frequent and distressing symptoms for all patients were tiredness, sleeping disturbances, and joint pain. Although fatigue has already been recognized as a very troublesome and frequent symptom, joint pain had not been identified in previous studies as an outstanding symptom. One of the reasons may be that we used the newer 45-item version of the MTSOSDS instead of the 36-item version in which joint pain was not yet included. Another possible explanation is that apart from representing an adverse effect of immunosuppressive medication, the symptom joint pain could reflect the age of the kidney transplant recipients. Moreover, newer immunosuppressive regimens may have different side-effect profiles, making certain items from previous versions of the instrument less relevant. Moon face, for example, which was very prevalent in an early 29-item version of the instrument,¹² seems to have become uncommon and less severe, probably as a result of diminished use of corticosteroids.

Congruent to previous research, we found several differences between symptom profiles of men and

women.⁴ In concordance with previous findings, women reported more frequent symptom occurrence (25 vs 19 items in quadrants 1 and 3), as well as higher distress levels (25 vs 22 items in quadrants 1 and 2). Also the number of frequent and distressing symptoms (quadrant 1) was much higher for women (17) than for men (10). The symptoms that differed most between the 2 sexes were changed appearance and anxiety. Surprisingly, increased hair growth on the face and body was not scored as very distressing by women, even though the symptom was rather common. For men, this item played, understandably, an even smaller role.

A limitation of this study is that our results are dependent on the chosen reference distribution. Rigid analysis requires an arbitrary choice of a standard distribution against which to make comparisons.¹³ In this study, we decided to create symptom profiles for men and women with the entire sample over all items as our reference group. This arrangement means that the symptom profiles of this study present a comparison within the measured symptoms of the MTSOSDS and

may be applied only to a kidney transplant population currently taking immunosuppressive medications.

Moreover, because women generally score higher than men on both dimensions, a slight overestimation of women's symptom experience and underestimation of men's symptom experience can be presumed. It is likely that this overestimation or underestimation was intensified by the greater number of men than women included in the sample, resulting in an additional convergence of the males' scores toward the center of the coordinate system, implying a less extreme symptom profile. And again, ideally, as has been done previously, the reference group would consist of a comparable sample of individuals who were not organ transplant recipients.¹² Even though the assessed symptoms are related to immunosuppressive medications, symptoms associated with adverse effects of other medications may have also contributed to patients' symptom experience in this study. As different numbers of medications prescribed might be a covariate that influences findings in view of differences between the sexes, we evaluated whether this factor differed between sexes (it did not). Thus the differences between the sexes seem to be due to factors other than concurrent medications prescribed (Table 1).

With this study, we suggest a new way of presenting symptom profiles that can be used in future research, for example, to compare kidney transplant populations with the general population, to compare symptom profiles depending on the immunosuppressive regimens, or to evaluate the development of symptom profiles over time. Furthermore, this study in which symptoms were ranked relative to one another, gives a reasonable idea of the clinical importance of symptoms. Fatigue remains, within the scope of measured symptoms, an important problem for all kidney transplant patients even a long time after the transplantation has been accomplished.

Whether joint pain and back pain are represented in this study in a higher proportion than in the general population of a similar age group and whether that higher proportion is due to comorbid conditions, kidney transplantation directly, or its medical regimens we cannot conclude from our results, but we can presume that these symptoms represent a long-term issue for kidney transplant patients. In addition, men especially seem to deal with impotence and anxiety and women with listlessness, mood swings, and changed appearance after transplantation. These findings give hints as to what should be addressed routinely by health

care professionals in established kidney transplantation after-care programs.

Conclusion

A 2-dimensional graphical display of data on symptom experience provides a new method for the presentation and evaluation of symptom profiles. Using this approach in future research might help clinicians and researchers to compare symptom profiles between different populations of patients.

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