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Weight changes after renal transplantation: a comparison between patients on 5-mg maintenance steroid therapy and those on steroid-free immunosuppressive therapy

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Abstract After renal transplantation (RTx), an increase in body weight (BW) is usually observed, in which corticosteroids may play an important role. However, the effects of a low maintenance dosage of corticosteroids on BW have not been studied longitudinally in RTx patients. The aim of this study was to compare changes in BW after RTx in patients on steroid- or steroid-free immunosuppressive therapy and to assess the relationship between post-transplant weight changes and other potentially important factors. The charts of 123 RTx patients (72 male, 51 female) were retrospectively examined for BW changes in the first 5 years after RTx. Sixty-six patients were on 5-mg maintenance steroid dose and 57 patients underwent steroid-free immunosuppression. Mean post-transplant BW gain was 3.0 ± 5.3 kg after 6 months, 3.9 ± 6.2 kg after 1 year and 6.2 ± 8.6 kg after 5 years. Weight gain in the first year after RTx was related neither to maintenance- nor to cumulative steroid dose, age, gender, occurrence of rejection, or renal function. Weight gain was, however, significantly related to pre-transplant BMI and dialysis modality. After the first year, weight gain was significantly and positively related only to the cumulative steroid dose. The course of weight gain in the first year after RTx turned out to be independent from factors such as maintenance- or cumulative steroid dose, age, gender, occurrence of rejection, and renal function; weight gain was, however, dependent on pre-transplant BMI and dialysis modality. After the first year, the weight course was significantly affected by cumulative steroid dose.

Keywords Post-transplant weight gain · Renal transplantation · Steroids · Steroid-free immuno suppression

Introduction

Malnutrition is common in patients with end-stage renal disease, and is strongly related to morbidity and mortality. The pathogenesis of malnutrition is multi-factorial, potential significant factors being reduction in appetite due to uremia, catabolic factors such as acidosis, loss of nutrients in the dialysate, and the presence of a chronic inflammatory state. Most of these factors are corrected by renal transplantation (RTx). The nutritional status may improve after RTx, as usually an increase in body weight is observed after RTx. However, it has also been shown that a large part of the weight gain after RTx is due to an increase in body fat mass [6, 7, 12, 19, 23], which may have untoward metabolic and cardiovascular effects [4, 9, 17]. The steroid immunosuppressive treatment after RTx may play a role in excessive weight gain and increased fat mass in renal transplant

patients. Glucocorticoids are known to have profound effects on adipocytes, resting energy expenditure and lipid oxidation, which can result in centripetal obesity (i.e., increased fat deposition in the peritoneum, mediastinum, and in subcutaneous sites on the face and the neck) [2, 19, 24]. Besides glucocorticoids, factors such as age, gender, pre-transplant BMI and dialysis modality, the occurrence and treatment of rejection, and post-transplant renal function may be significant in the pathogenesis of weight changes after RTx.

To date, the effects of low maintenance dosage of corticosteroids on body weight after RTx have not been studied longitudinally. In this study, we therefore analyzed weight changes after RTx in relation to maintenance- and cumulative steroid dose. The relationship between other factors possibly affecting body weight (as mentioned above) and post-transplant changes in body weight was also assessed.

Materials and methods

Materials

The charts of all patients who received a kidney graft in our center between January 1982 and December 1994 were examined for weight changes in the first 5 years after RTx. In this period, 333 patients had undergone transplantation. Of these patients, 50 had had to (re)start dialysis, and 54 died within 5 years of undergoing transplantation. A further 33 patients underwent transplantation in the pre-cyclosporine era and were using azathioprine and a high maintenance dose of prednisolone (≥10 mg/day). Yet another 15 patients participated in a clinical trial and were treated with tacrolimus immunosuppression. In 82 patients either a non-regular immunosuppressive regimen was used (due to, among other things, treatment in hospitals elsewhere, a protocol violation) or follow-up was lost. Complete data of 123 transplant patients were available for analysis.

Of these 123 patients, 118 had received cadaveric renal allografts and five had received living-(un)related donor renal allografts. Reasons for kidney failure were chronic glomerulosclerosis (31.7%), pyelonephritis (4.9%), nephrosclerosis (4.1%), polycystic kidney disease (17.9%), diabetes (8.1%), and other (33.3%). Before RTx, 78 patients were on hemodialysis (HD) and 42 patients were on continuous ambulant peritoneal dialysis (CAPD); three patients did not undergo renal replacement therapy.

Since the introduction of cyclosporine, the standard immunosuppressive regimen at our center has been cyclosporine and low-dose prednisolone (10 mg/day) for recipients of first grafts. The prednisolone dose is reduced to 7.5 mg/day at month 1 and to 5 mg/day at month 3. In recipients without rejection, the prednisolone dose is further tapered to 0 mg over the next months. For highly immunized recipients (PRA > 85%) and re-transplant patients, azathioprine (± 1 mg/kg body weight) is added to the above regimen, and the dose of prednisolone is tapered to and maintained at 5 mg/day.

Of the 123 RTx patients, 57 underwent cyclosporine mono-therapy without prednisolone; cyclosporine mono-therapy was started at 7.3 ± 2.6 months after RTx (range 3.7–15.4 months). Further 66 patients were treated with cyclosporine and a maintenance prednisolone dose of 5 mg/day. Of these 66 patients, 46 experienced acute rejection within 6 months of RTx (the 5-mg pred/rej+ group); in 15 of these 46 patients azathioprine was added to the cyclosporine and 5 mg prednisolone immunosuppressive therapy. The remaining 20 (all re-transplant- or highly immunized patients) did not experience any rejections (the 5-mg pred/rej− group). The steroid maintenance dose was reached at 3.5 ± 1.5 months after RTx (range 1.4–7.8 months) in the 5 mg pred/rej+ group and at 3.6 ± 2.9 months (range 1.4–10.1 months) in the 5 mg pred/rej− group.

Clinical characteristics of the patients in the 0-mg maintenance steroid, the 5-mg pred/rej+, and the 5-mg pred/rej− groups are shown in Table 1. Groups were comparable for age, body weight, and BMI before RTx; creatinine clearance (calculated by the formula of Cockcroft [1]) 1 year after RTx was significantly better in the 5-mg pred/rej− group than in the 0-mg and 5-mg pred/rej+ groups.

Methods

In this retrospective, longitudinal study, we initially studied changes in body weight after RTx. Then, the relationship between post-transplant weight changes and the maintenance steroid dose was assessed. For this purpose, weight changes in RTx patients on 0- and 5-mg maintenance prednisolone dose were compared. Of these, the group of patients undergoing 5-mg prednisolone maintenance therapy was further divided into patients who experienced rejection episodes (rej+ group) and patients who did not (rej− group). We did this because patients experiencing rejection were receiving steroid boluses, which increased the cumulative steroid dose in the rej+ group (Table 2). Finally, the relationship between age, gender, pre-transplant BMI, pre-transplant dialysis modality (i.e., HD or CAPD), renal function (creatinine clearance), acute rejection (i.e., occurrence of acute rejection within 6 months post-transplantation), the cumulative steroid dose, and post-transplant weight changes, was also investigated.

Baseline body weight was measured at admission, prior to transplantation; CAPD patients were measured while their abdomen was empty. In the first year after RTx, the body weight of the patients was measured at months 1, 2, 3, 6, 9, and 12. Thereafter, body weight was assessed each year (24, 36, 48 and 60 months after transplantation). Patients were weighed (wearing only underwear) during routine visits to the nephrology outpatient clinic in our hospital.

Table 1 Clinical characteristics of the RTx patients in the 0 mg prednisolone, the 5 mg pred/rej- and 5 mg pred/rej+ group (mean ± SD)

Parameters	0 mg ($n = 57$)	5 mg/rej − ($n = 20$)	5 mg/rej+ ($n = 46$)
Age (years)	47.6 ± 12.3	45.7 ± 11.4	42.9 ± 12.8
Gender (M/F)	32 / 25	11 / 9	29 / 17
Body weightbefore RTx (kg)	66.0 ± 10.8	67.7 ± 12.7	71.0 ± 15.6
BMI before RTx (kg/m^2)	22.9 ± 3.0	23.2 ± 3.1	24.6 ± 4.6
Creatinine clearance (ml/min)[a]	55.4 ± 18.4	71.4 ± 17.3[b]	58.9 ± 20.1

[a]creatinine clearance one year after RTx
[b]$P < 0.01$ compared to 0 mg group; $P < 0.05$ compared to 5 mg/rej+ group

Table 2 Cumulative steroid doses (mg) in the 0 mg prednisolone, the 5 mg pred/rej- and 5 mg pred/rej+ group [mean ± SD (median)]

Time after RTx	0 mg ($n=57$)	5 mg / rej − ($n=20$)	5 mg / rej + ($n=46$)
1 month	384.0 ± 69.8 (377.5)*	416.0 ± 63.9 (393.7)*	1628.8 ± 1457.4 (487.5)
2 months	624.0 ± 73.9 (612.5)*	660.5 ± 53.5 (666.3)*	2020.6 ± 1460.8 (1052.5)
3 months	800.5 ± 107.2 (775.0)*	863.1 ± 82.5 (857.5)*	2308.8 ± 1473.2 (2003.8)
6 months	1070.0 ± 209.1 (1055.0)*	1389.4 ± 195.8 (1330.0)*	2808.5 ± 1482.5 (2450.0)
12 months	1198.7 ± 375.8 (1058.8)* #	2320.7 ± 252.2 (2240.0)*	3842.4 ± 1470.8 (4093.8)
60 months	1293.8 ± 595.8 (1063.8)* #	9639.4 ± 260.9 (9549.3)*	11361.5 ± 1796.0 (11408.8)

*$P < 0.001$ compared to 5 mg/rej + group
#$P < 0.001$ compared to 5 mg/rej-group

Statistics

Results were expressed as mean ± SD. Comparisons for the clinical characteristics between the RTx patients in the 0-mg, 5-mg pred/rej−, and 5-mg pred/rej + groups were performed by means of one-way ANOVA analysis; pairwise multiple comparisons were corrected via post-hoc Bonferroni tests.

Post-transplant changes in body weight within the 0-mg-, 5-mg pred/rej−, and 5-mg pred/rej + groups (= within factor = factor 'time'), as well as within-patient differences between these three groups (= between factor = factor 'group'), were analyzed by means of two-way repeated measures ANOVA. In this way the effects of the factor 'time', 'group', and of the interaction term 'time by group', were determined. A significant 'time'-factor means that body weight significantly changes over the time period; a significant 'time by group' interaction term points to differences in body weight course between the 0-mg, 5-mg pred/rej− and 5-mg pred/rej + group. Reversed Helmert contrasts were sometimes used to test differences with the baseline. Apart from this, body weight 12 months after RTx was used as baseline in the analysis of post-first-year changes in body weight.

Possible disturbing or modifying effects on post RTx weight course caused by different variables were analyzed next, by means of two-way repeated measures ANCOVA if the potential confounding variable was of interval or ratio measurement level, and by two-way repeated measures ANOVA if a potential confounding factor was involved. Confounding factor interrelations appeared at one instance so relevant for weight changes that both were introduced simultaneously within the ANOVA model: the interaction term of both confounders with weight changes was inspected. Statistical analysis was performed by SPSS-PC for Windows, version 9.0.

Results

Weight gain after renal transplantation

The mean baseline (pre-transplant) body weight in the RTx patients ($n=123$) was 68.2 ± 13.2 kg. In the first month after RTx, body weight decreased significantly to 67.4 ± 12.7 kg ($P < 0.05$). After this, patients started to gain weight. Two months after RTx, patients returned approximately to their baseline body weight. After the first 3 months, the body weight of the RTx patients had increased to 72.1 ± 12.0 kg (+6.7 ± 9.9%) 1 year after RTx ($P < 0.001$) and to 74.4 ± 14.0 kg (+10.0 ± 13.5%) 5 years after RTx ($P < 0.001$). The F-ratio for weight gain (= factor 'time') in the first year after RTx was $F_{2,262} = 62.35$ ($P < 0.001$), and for weight gain after the first year it was $F_{3,331} = 11{,}38$ ($P < 0.001$).

Steroid immunosuppression and post-transplant weight changes

Post-transplant changes in body weight in the 0-mg, 5-mg pred/rej−, and 5-mg pred/rej + groups are given in Fig. 1. The F-ratio for weight gain in the first year after RTx was $F_{2,256} = 55.47$ ($P < 0.001$) and for weight gain after the first year was $F_{3,331} = 10.34$ ($P < 0.001$). Body weight course in the first year after RTx, and post-first-year body weight course were not significantly different between patients in the 0-mg, 5-mg pred/rej−, and 5-mg pred/rej + groups. In the first year after RTx, body weight significantly increased from 67.8 ± 12.7 kg (baseline) to 72.8 ± 11.9 kg (+8.5 ± 11.0%) in the 5-mg pred/rej− group ($P < 0.01$), from 71.0 ± 15.6 kg (baseline) to 74.3 ± 14.5 kg (+5.8 ± 10.7%) in the 5-mg pred/rej + group ($P < 0.01$), and from 66.0 ± 10.8 kg (baseline) to 70.0 ± 9.4 kg (+6.8 ± 8.8%) in the 0-mg group ($P < 0.001$). After the first year, body weight gradually increased to 75.2 ± 13.8 kg (+3.1 ± 7.3%) in the 5-mg rej− group ($P = 0.07$), to 77.9 ± 16.8 kg (+4.7 ± 8.0%) in the 5-mg/rej + group ($P < 0.001$), and to 71.2 ± 10.8 kg (+1.7 ± 7.0%) in the 0-mg group ($P = 0.08$) at 5 years after RTx.

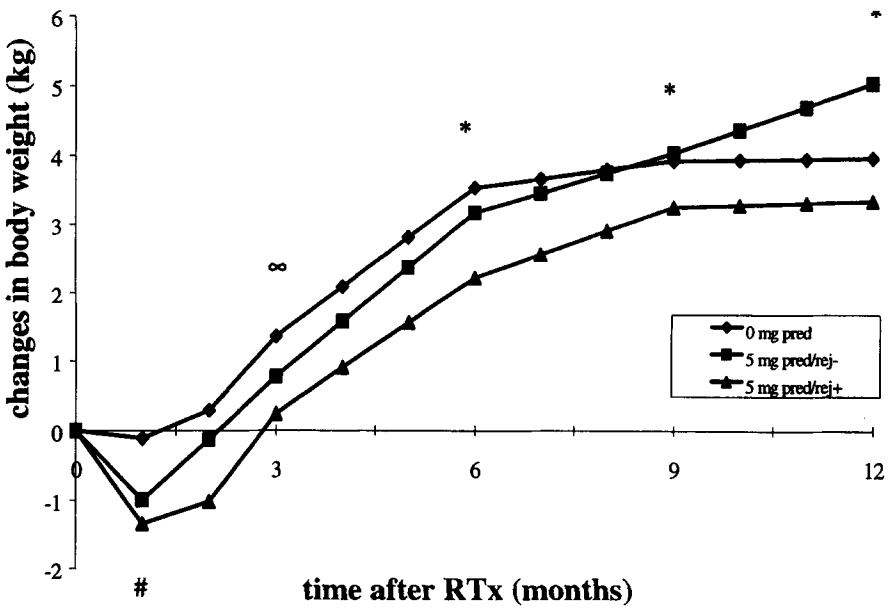
Cumulative doses of steroids also had no relationship whatsoever with the post-transplant weight course of RTx patients within the first year after RTx. The cumulative steroid dose, however, did significantly affect the linear trend for weight course after the first year after RTx: the higher the cumulative steroid dose, the higher the weight gain.

Relationship between age and gender and post-transplant weight changes

The post-transplant course of body weight was not related to the age of the RTx recipient, nor was it significantly different for men and women.

Relationship between pre-transplant BMI, dialysis modality and post-transplant weight changes

At baseline, 16 RTx patients (13.0%) had a BMI < 20 kg/m^2, 73 patients (59.3%) had a BMI between 20



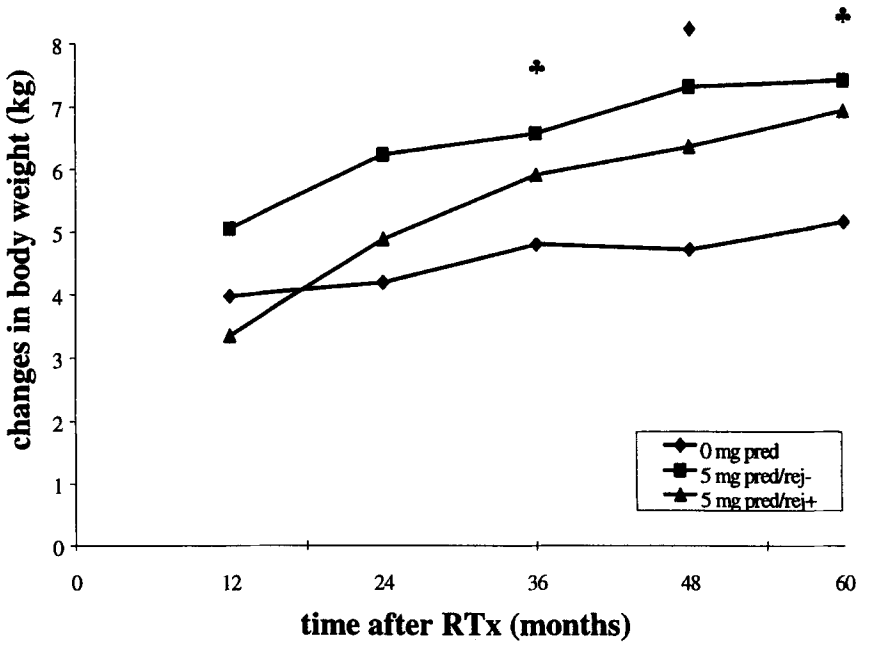


Fig. 1 Weight changes in the first year and after the first year post RTx in the 0-mg, 5-mg pred/rej−, and 5-mg/rej + groups (* $P<0.05$ compared with baseline in the 0-mg, 5-mg pred/rej−, and 5-mg pred/rej + groups; # $P<0.05$ compared with baseline only in the 5-mg pred/rej + group, ∞ $P<0.05$ compared with baseline only in the 0-mg pred group; ♣ $P<0.05$ compared with month 12 only in the 5-mg pred/rej + group; ♦ $P<0.05$ compared with month 12 only in the 5-mg pred/rej + and 5-mg pred/rej− groups

and 25 kg/m^2, and 32 patients (26.0%) had a BMI > 25 kg/m^2; mean body weight in these groups was 52.9 ± 5.5 kg, 65.4 ± 8.6 kg and 83.1 ± 10.7 kg, respectively ($P<0.001$). Weight gain in these three groups during the first year after RTx appeared to be significantly different ($F_{\text{time×BMI-group}(5,268)}=7.57$; $P<0.001$): patients with a BMI > 25 kg/m^2 had a significantly lower weight gain (0.8 ± 8.0%) than patients with a BMI between 20 and 25 kg/m^2 (7.4 ± 9.2%, $P<0.05$) and patients with a BMI < 20 kg/m^2 (16.0 ± 8.3%, $P<0.001$ compared with BMI > 25 and BMI 20–25 kg/m^2). Next to this result, at baseline, the 78 patients who had HD had a significantly lower weight than the 42 patients who had CAPD (65.8 ± 12.1 kg vs 73.0 ± 14.2 kg, $P<0.01$). Weight gain during the first year after RTx in these two groups was also significantly different ($F_{\text{time×dialysis modality}(2,256)}=4.02$, $P<0.05$): patients with CAPD had a significantly lower weight gain than patients with HD. However, as shown in Fig. 2, the latter result seems to be valid only for RTx patients with

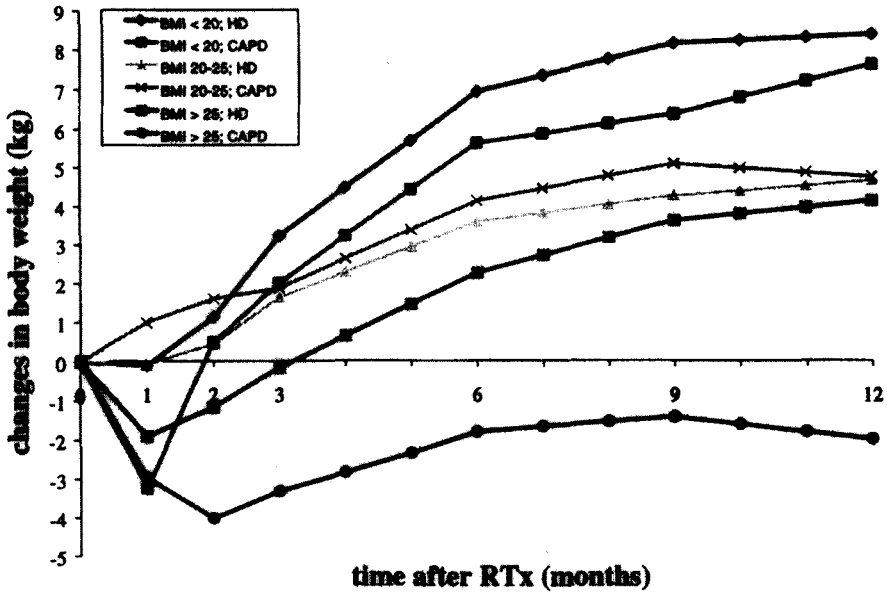


Fig. 2 Post-transplant body weight in RTx patients with a pre-transplant BMI <20 kg/m^2 ($n=16$), 20–25 kg/m^2 ($n=73$), and >25 kg/m^2 ($n=32$)

a BMI >25 kg/m^2. Pre-transplant BMI was highly related to pre-transplant dialysis modality (mean BMI in HD versus CAPD patients was 23.0 ± 3.2 kg/m^2 vs 24.8 ± 4.5 kg/m^2, $P<0.05$). So, as a next step, we introduced both BMI group and dialysis modality as factors in the ANOVA weight-gain model. The interaction effect 'time × dialysis modality × BMI group' was, however, not significant ($F_{5,257}=2.08$, $P=0.08$). Thus, in conclusion, patients with a low pre-transplant BMI gain significantly more weight in the first year after RTx than patients with higher BMIs, irrespective of pre-transplant dialysis modality. Neither pre-transplant BMI nor dialysis modality had any effect on the body weight course after the first year.

Relationship between acute rejection and post-transplant weight changes

Forty-six patients experienced acute rejection within 6 months of RTx. On average, the rejection episodes occurred 12.4 ± 10.9 (range 1–56; median 8.0) days post-transplantation. The body weight course in the first year after RTx and the weight course after the first year were not significantly different for patients with or without a history of acute rejection.

Relationship between renal function and post-transplant weight changes

In the first year after RTx, at none of the time points of measurement was the average weight gain significantly related to the creatinine clearance. The mean creatinine clearance of the patients ($n=123$) 1 year after RTx was 59.3 ± 19.5 ml/min. To facilitate the analysis, we divided the RTx patients into two groups, to assess the relationship between renal function (i.e., creatinine clearance) and post-transplant weight gain. Group I consisted of RTx patients with a creatinine clearance ≤ 50 ml/min 1 year after RTx ($n=45$); group II consisted of patients with a creatinine clearance >50 ml/min 1 year after RTx ($n=78$). The body weight course in the first year after RTx and the post-first-year weight course were not significantly different for groups I and II.

Discussion

We studied the changes in body weight after RTx. Furthermore, the relationship between post-transplant weight changes and the maintenance prednisolone dose was assessed. Relationships between post-transplant weight changes on the one hand, and age, gender, pre-transplant BMI, pre-transplant dialysis modality, renal function, acute rejection, and the cumulative dose of steroids on the other hand, were also investigated.

In the first month after RTx, patients on the average lost body weight. This could be due to catabolic effects of surgery, loss of excess fluid, delayed graft function, or decreased dietary intake in the early post-transplant period. After the first month after RTx, patients started to gain weight, which resulted in a mean increase in body weight of 3.0 kg at 6 months after RTx, 3.9 kg at 1 year, and 6.2 kg at 5 years after RTx. Post-transplant weight gain was, however, relatively low when compared with the weight gain reported in other studies [3, 13, 14, 16].

One explanatory factor might be the relatively low steroid dose in our study. Moore and Gaber [14] found a mean weight gain of 4.0 kg during the first 6 months after RTx in a group of patients who were treated with 0.5 mg steroids/kg ideal body weight (IBW) in the first 3 months after RTx and 0.2 mg steroids/kg IBW after the first 3 months. Merion et al. [13] found an average weight gain of 8.9 kg in non-obese patients and 14.2 kg in obese patients during the first year after RTx; both the obese and non-obese patients underwent immunosuppressive therapy with high dosages of corticosteroids (> 10 mg/day), cyclosporine and azathioprine.

Excessive weight gain, a major problem for many RTx patients, is associated with an increased risk of metabolic and cardiovascular complications, a major cause of morbidity and mortality in renal transplant patients [4, 9, 11, 17]. Some weight gain might be favorable in patients who were malnourished at the point of transplantation. In an earlier prospective pilot study [21] however, we observed that weight gain in the early post-transplant period (at least until 6 months after RTx) was predominantly due to an increase of the body fat mass, and not to an increase of the lean body mass.

In the present study, no differences were found in the body weight course of patients in the 0-mg, 5-mg pred/rej− and 5-mg pred/rej+ groups in the first year and after the first year after RTx, and no relationship was observed between first year post-transplant weight gain and the cumulative steroid dose. Cumulative steroid dose was, however, significantly and positively related to post-first-year weight gain.

Johnson et al. [8] did not find a significant relationship between post-transplant weight gain and cumulative steroid dose 1 year after RTx either, whereas the cumulative dose was substantially higher than that in our study. Conversely, Ratcliffe et al. [18] found, in a randomized controlled trial, that RTx patients allocated to the prednisolone-withdrawal group had a slight but significant reduction in body weight, whereas over the same period there was a slight increase of body weight in the control group. Hagan and colleagues [5] found that successful withdrawal of maintenance corticosteroids in the first year after heart transplantation decreased post-transplant weight gain. On the other hand, neither Lake et al. [10] nor Olivari et al. [15] observed significant differences in weight gain after heart transplantation between patients undergoing prednisolone therapy and patients tapered from prednisolone therapy. Evidently, the results are conflicting, and more prospective studies are needed to assess definitively the influence of low-dose steroids on post-transplant weight gain.

In this study, only body weight was assessed. Therefore, differences in body composition between the various prednisolone groups in the study cannot be excluded. However, in an earlier cross-sectional study on 75 RTx patients in our center, no differences in fat mass were observed whether the daily maintenance steroid dose was 10-, 5-, or 0-mg prednisolone. Furthermore, no relationship between the cumulative dose of prednisolone and body composition was observed [20]. Nevertheless, the increase in body fat between 3 and 6 months after RTx tended to be lower in patients undergoing steroid-free immunosuppressive therapy than in patients receiving steroid immunosuppressives [22]. Prospective randomized studies are therefore needed to assess more precisely the influence of low-dose maintenance steroid therapy on weight gain and body composition in renal transplant patients.

We did not find a relationship between age and gender, respectively, and post-transplant weight gain. This is in contrast with the study by Johnson et al. [8] who found a comparable weight gain in men and women during the first year after RTx, although women continued to gain weight after the first year and men remained relatively stable. Johnson et al. also found a larger weight gain in younger patients (18–29 years) than in middle-aged (30–49) and older patients (> 50). Moore and Gaber [14] found no difference in weight gain between men and women in the first 6 months after RTx.

A difference in weight course between patients with or without rejection episodes or in patients with well-functioning grafts or with decreased renal function, might be expected. Factors accompanied by rejection episodes and decreased renal function, such as (prolonged) hospitalization, increased stress, prolonged effects of uremia, catabolism, feeling of malaise, or decreased appetite, might affect weight course after RTx. In the present study, however, we did not find any relationship between post-transplant weight changes and acute rejection or renal function, which is consistent with the results of Johnson et al. [8]. In contrast, Moore and Gaber [14] noticed that the occurrence of rejection episodes in patients who lost body weight in the first 6 months after RTx was significantly higher than in patients who gained weight during this period.

In the present study, we initially found differences in weight course in the first year after RTx between patients with a pre-transplant BMI < 20 kg/m^2, BMI 20–25 kg/m^2, and BMI > 25 kg/m^2 and also between pre-transplant HD and CAPD patients, the latter experiencing a significantly lower weight gain than the HD patients. Although pre-transplant BMI was significantly higher in CAPD patients than in HD patients, no significant interaction effect of pre-transplant BMI and pre-transplant dialysis modality on post-transplant weight course appeared to be in existence. The larger increase in body weight in patients with low BMI might be explained by an improvement in their nutritional state, although this cannot be definitively determined from the available data. This again highlights the importance of detailed data on body composition in future nutritional studies.

In conclusion, renal transplant patients started to gain weight from the first month after RTx, after losing weight in the first month. In the first year after RTx, the increase in body weight was related neither to maintenance- nor cumulative steroid dose, whereas in the later post-transplant period, cumulative steroid dose appeared to have a significant effect on body weight increase. Post-transplant weight gain was not related to age, gender, episodes of rejection or renal function. Weight gain in the first year after RTx was, however, significantly related to pre-transplant BMI and dialysis modality. More detailed data are needed to definitively assess the influence of relatively low maintenance doses of corticosteroids on post-transplant body weight course and body composition.

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