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ORIGINAL ARTICLE

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The influence of early steroid withdrawal on body composition and bone mineral density in renal transplantation patients

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Abstract Corticosteroid treatment may have an important effect on body composition and bone mineral density (BMD) in renal transplantation (RTx) patients. We investigated the effect of early steroid withdrawal on body composition and BMD of RTx patients in a prospective design. Post-transplant immunosuppression consisted of tacrolimus, mycophenolate mofetil, and prednisolone. Three months after RTx, 27 patients participating in a multi-center trial were randomized either to continue steroids (at a dose of 10 mg/day, $n=17$; steroid+) or be withdrawn from steroids within 2 weeks ($n=10$; steroid–). Body composition and BMD (lumbar spine (L2–L4) and femoral neck) were measured by dual-energy X-ray absorptiometry (DEXA) just before and 3 months after randomization. With regard to body composition, fat mass tended to increase in the steroid+ group (1.1 ± 2.3 kg; $P=0.084$), but did not change in the steroid– group. Increase in body fat percentage tended to be higher ($P=0.08$) in the steroid+ group ($0.6\pm2.7\%$) than in the steroid– group ($-0.7\pm2.1\%$). The change in lean body mass was not significantly different between the two groups. BMD of the lumbar spine and femoral neck decreased significantly in the steroid+ group ($-1.4\pm3.2\%$ and $-2.3\pm2.9\%$, respectively, $P<0.05$) while no changes were observed in the steroid– group. The change in BMD of the lumbar spine was significantly different between the steroid+ and the steroid– group, whereas the change in BMD of the femoral neck was not significantly different. Thus, the increase in fat mass tended to be higher in the group continuing on steroids, though not significant, due to large inter-individual variation. In general, the effect of early steroid withdrawal on body composition after RTx appears to be modest. In addition, early steroid withdrawal seems to have beneficial effects on BMD in RTx patients, especially in the lumbar region.

Keywords Renal transplantation · Steroid withdrawal · Body composition · Bone mineral density · Osteoporosis

Introduction

Corticosteroids are an integral part of maintenance immunosuppressive therapy after renal transplantation (RTx). However, the long-term use of corticosteroids is associated with many adverse sequelae. Two major complications in RTx patients, in which use of steroids has been implicated, are excessive weight gain and osteoporosis after transplantation. Whereas the health risks of osteoporosis are clear, excessive weight gain

may also contribute to morbidity. In a previous study [15], we showed that early weight gain after RTx was predominantly due to an increase in body fat mass, which may represent a further risk factor for the persistently high cardiovascular morbidity in RTx patients.

With regard to the relation between bone disease and corticosteroids, there is general agreement that doses of prednisolone higher than 7.5 mg/day for longer than 3 months will result in bone loss in the vast majority of patients. However, it has never been investigated whether early withdrawal of corticosteroids has an important beneficial effect on bone loss after RTx.

The influence of relatively low doses of steroids on body composition is less clear. Surprisingly, in a previous cross-sectional study, we did not find differences in body composition between patients with maintenance steroid doses of 0, 5, and 10 mg [14], whereas in a retrospective analysis no differences between patients with these different steroid maintenance doses were observed in weight gain either, over a 5-year period [16]. Nevertheless, higher steroid doses are generally used early after RTx, which are likely to have an important effect on body composition. No previous study, however, has addressed the effect of early steroid withdrawal on body composition in RTx patients. With regard to these considerations, the aim of the study was to assess the effect of early steroid withdrawal on bone mineral density (BMD) and body composition in RTx patients early after transplantation.

Patients and methods

Patients

Forty-two patients participating in a multi-center trial within the first 6 months after RTx were included. Exclusion criteria for the present study were episodes of acute rejection (greater than Banff II) or severe intercurrent diseases. Of the 42 patients, 15 experienced either severe infection or rejection and were not eligible for further study. Therefore, body composition was assessed in 27 RTx patients (21 male, six female). In four patients (one male, three female), measurement of BMD was not possible for technical reasons. Patient characteristics are given in Table 1. All patients had adequate diuresis and were clinically euvolemic. None of the patients received calcium, vitamin D, or bisphosphonate treatment.

As part of the multi-center trial, post-transplant immunosuppression consisted of tacrolimus (plasma level 15–20 ng/ml during the first 2 weeks, 10–15 ng/ml from day 14 to day 30, and 7–10 ng/ml thereafter), mycophenolate mofetil (MMF, 1,000 mg/day), and prednisolone (20 mg/day from day 2 onward). On day 14, the prednisolone dose was diminished to 15 mg/day and on day 28 to

Table 1 Clinical characteristics of the RTx patients in the steroid+ and steroid– groups at the time of randomization. Values are given as mean ± SD (median)

Characteristic	Steroid+ group ($n=17$)	Subgroup steroid+/ MMF+ ($n=9$)	Subgroup steroid+/ MMF– ($n=8$)	Steroid– group ($n=10$)
Age (years)	52.4±13.6 (57.5)	50.3±17.2 (57.5)	54.8±8.5 (55.7)	56.3±17.2 (60.9)
Male/female	14/3	6/3	8/0	7/3
Creatinine clearance (ml/min)[a]	54.4±12.8 (50.6)	54.9±12.1 (55.3)	53.9±14.4 (49.0)	63.1±16.3 (64.7)
Parathyroid hormone (pmol/l)[b]	10.5±7.8 (8.5)	13.5±9.4 (10.2)	7.4±4.7 (5.3)	9.4±7.3 (6.8)
Albumin (g/l)[b]	40.7±3.8 (41.1)	41.2±2.9 (41.2)	40.0±4.8 (39.8)	40.4±3.3 (40.1)
Calcium (mmol/l)[b]	2.53±0.1 (2.53)	2.52±0.12 (2.52)	2.54±0.13 (2.55)	2.58±0.2 (2.53)
Body composition				
Body weight (kg)	71.9±7.8 (69.6)	74.4±8.4 (74.1)	69.1±6.3 (69.1)	76.9±13.6 (75.6)
Body mass index (kg/m^2)	24.2±1.9 (24.1)	24.8±2.3 (25.9)	23.5±1.3 (23.1)	26.0±4.0 (25.4)
Fat mass (kg)	20.5±6.5 (20.4)	23.3±7.0 (22.0)	17.3±4.3 (17.0)	23.1±6.4 (23.1)
Lean body mass (kg)	51.4±8.6 (54.8)	51.1±10.7 (54.8)	51.8±6.3 (52.3)	53.8±10.0 (53.3)
Body fat (%)	28.5±8.9 (27.5)	31.6±1.3 (28.7)	25.1±5.8 (25.6)	30.0±6.3 (30.4)
BMD				
Lumbar spine				
BMD (g/cm^2)	1.219±0.19 (1.229)	1.217±0.24 (1.229)	1.220±0.09 (1.221)	1.165±0.27 (1.210)
Z score	0.3±1.2 (0.2)	0.4±1.4 (0.2)	0.3±0.9 (0.2)	–0.3±2.2 (0.1)
T score	–0.1±1.5 (–0.1)	–0.1±1.9 (–0.9)	–0.1±0.9 (–0.1)	–0.6±2.3 (–0.3)
Femoral neck				
BMD (g/cm^2)	0.865±0.12 (0.857)	0.842±0.14 (0.801)	0.899±0.09 (0.870)	0.872±0.19 (0.893)
Z score	–0.6±0.7 (–0.8)	–0.8±0.7 (–1.1)	–0.4±0.7 (–0.6)	–0.6±1.5 (–0.5)
T score	–1.5±0.8 (–1.4)	–1.6±0.9 (–2.0)	–1.2±0.7 (–1.2)	–1.4±1.5 (–1.4)

[a]Assessed by Cockcroft formula
[b]Routine laboratory assessment

10 mg/day. Three months after RTx, patients were randomized to continue steroids (at a dose of 10 mg/day, $n=17$) or be withdrawn from steroids within 2 weeks ($n=10$). Eight of the 17 patients continuing steroids were randomized to stop having MMF 3 months after RTx. The multi-center trial was completed 6 months after RTx. After this period, steroids and/or MMF were tapered; tapering of steroids and/or MMF was, however, not performed in a standardized manner. Clinical characteristics of the patients randomized to continue steroids (the steroid+ group) or be withdrawn from steroids (the steroid– group) are shown in Table 1.

Methods

Body composition and BMD of the lumbar spine and femoral neck were measured by dual-energy X-ray absorptiometry (DEXA) at the time of randomization (i.e., 3 months after RTx) and 6 months after RTx. The equipment used in this study was DPX-L (Lunar Radiation, Madison, Wis.).

DEXA measurements were performed in a standard fashion while the patient was lying in a supine position on a table. From an X-ray source and K-edge filter below the patient, X-ray beams of stable energy radiation of 38 and 70 keV were emitted. Attenuation of the X-rays was measured with a detector situated above the patient. Transverse scans of the body were made from top to toe. For each transverse scan, about 120 pixel elements with a size of approximately 5×10 mm yielded data on the attenuation ratio. Approximately 40%–45% of the pixels over the body contain bone and soft tissue, 55%–60% containing soft tissue alone [8]. Bone mass was estimated from the ratio of attenuation at low energy peaks relative to that at high energy peaks through bone-containing pixels after correction for the overlying soft tissue. The composition of soft tissue was estimated by the ratio of beam attenuation at lower energy relative to that at higher energy in soft tissue pixels; this ratio is inversely and linearly related to fat percentage [7, 8]. The coefficient of variation of DEXA measurements is 1.1%.

Statistics

Because of the small group of patients studied and the fact that assumptions of normal distribution of variables were not met, non-parametric statistical tests were used for comparisons. The RTx patients with steroid immunosuppression and the patients with steroid-free immunosuppression were compared for changes in body composition and BMD by means of Mann-Whitney tests. Changes within the different groups were assessed with Wilcoxon signed rank tests. Data were expressed as mean ± SD (median). Statistical analysis was performed with SPSS for Windows, version 9.0.

Results

Clinical characteristics of the RTx patients at the time of randomization are given in Table 1. Seventeen patients (14 male, three female) were randomized to continue steroids (the steroid+ group) whereas ten patients (seven male, three female) were randomized to be withdrawn from steroids within 2 weeks (the steroid– group). At the time of randomization, the steroid+ and steroid– groups were comparable for age, creatinine clearance, and levels of parathyroid hormone, albumin, and calcium. The steroid groups were also comparable for body composition, BMD of the lumbar spine, and BMD of the femoral neck. All patients included completed the study; none of them suffered periods of acute rejection or had serious abdominal complaints (i.e., pain, dyspepsia, or diarrhea) or intercurrent diseases during the study period.

Table 2 Changes in body composition and BMD in RTx patients with and without steroids. Values are given as mean ± SD. Changes (i.e., Δ) are the mean of the individual changes in the period between 3 and 6 months after transplantation

Parameter	Steroid– group ($n=10$)	Steroid+ group ($n=17$)	Subgroup steroid+/ MMF+ ($n=9$)	Subgroup steroid+/ MMF– ($n=8$)
Body composition				
Δ body weight (kg)	0.7 ± 2.3	1.8 ± 2.7[a]	1.7 ± 3.7	1.8 ± 0.8[a]
Δ fat mass (kg)	–0.4 ± 1.4	1.1 ± 2.3	1.5 ± 2.9	0.7 ± 1.6
Δ lean body mass (kg)	1.0 ± 2.7	0.6 ± 2.3	0.2 ± 2.9	1.1 ± 1.5[a]
Δ body fat (%)	–0.7 ± 2.1[a]	0.6 ± 2.7	1.0 ± 3.1	0.3 ± 2.4
BMD				
Lumbar spine				
Δ BMD (%)	1.9 ± 4.2[d]	–1.4 ± 3.2[a]	–1.6 ± 4.0	–1.1 ± 1.9
Δ T-score	0.1 ± 0.3[e]	–0.2 ± 0.3[b]	–0.2 ± 0.4	–0.2 ± 0.2
Δ Z-score	0.1 ± 0.2[d]	–0.3 ± 0.3[a]	–0.4 ± 0.4	–0.2 ± 0.3
Femoral neck				
Δ BMD (%)	–0.3 ± 6.2	–2.3 ± 2.9[a]	–1.1 ± 3.0	–4.0 ± 1.8[a,f]
Δ T-score	0.0 ± 0.3	–0.2 ± 0.3[a]	–0.1 ± 0.2	–0.4 ± 0.2[a,f]
Δ Z-score	0.0 ± 0.4	–0.2 ± 0.2[c]	–0.1 ± 0.2	–0.4 ± 0.1[a,f]

[a] $P<0.05$ compared to time of randomization
[b] $P=0.053$ compared to time of randomization
[c] $P<0.01$ compared to time of randomization
[d] $P<0.01$ compared to steroid+ group
[e] $P<0.05$ compared to steroid+ group
[f] $P<0.05$ compared to steroid+/MMF+ group

Changes in body composition and BMD in the steroid+ and steroid– groups are given in Table 2. Body weight increased significantly by 1.8 ± 2.7 kg in the steroid+ group, while it did not change significantly in the steroid– group. Fat mass tended to increase in the steroid+ group (1.1 ± 2.3 kg, $P = 0.084$), but did not change in the steroid– group. In both steroid groups, no changes in lean body mass were observed. The body fat percentage in the steroid+ group did not change; in the steroid– group, however, the body fat percentage decreased significantly (–0.7 ± 2.1 kg, $P < 0.05$). Changes in body weight, fat mass, and lean body mass were not significantly different between the steroid+ and steroid– groups. In contrast, the change in body fat percentage tended to be different between the two steroid groups ($P = 0.08$).

BMD and Z score of the lumbar spine decreased significantly in the steroid+ group (–1.4 ± 3.2% and –0.3 ± 0.3%, respectively, P values both < 0.05); the T score of the lumbar spine tended to decrease (–0.2 ± 0.3%, $P = 0.053$). This was in contrast to the steroid– group, in which no significant changes in BMD, Z score, and T score of the lumbar spine were observed. However, the change in BMD, Z score, and T score of the lumbar spine was significantly different between the two steroid groups.

Moreover, BMD, Z score, and T score of the femoral neck decreased significantly in the steroid+ group (–2.3 ± 2.9%, –0.2 ± 0.2%, and –0.2 ± 0.3%, respectively; $P < 0.05$, $P < 0.01$, and $P < 0.05$, respectively). In the steroid– group no significant changes in BMD, Z score and T score of the femoral neck were observed. Changes in BMD, Z score, and T score were not significantly different between the two steroid groups.

Discussion

In this prospective randomized study, the increase in body fat percentage tended to be lower in patients with early steroid withdrawal than in patients continuing steroid immunosuppression, whereas the loss of vertebral bone mass was significantly higher in patients continuing steroids than in the steroid-free group.

The effect of steroid treatment on fat mass could be explained by reduced lipolysis induced by corticosteroids. In acute hypercortisolemia, steroids acutely reduced lipolysis in subcutaneous fat [10], whereas in a study by Steiger et al. in RTx patients, daily prednisone doses were inversely related to lipid oxidation [12]. The present data are somewhat in contrast to our previous cross-sectional study, in which no difference in body composition was observed between RTx patients on maintenance steroid doses of 0, 5, and 10 mg, respectively; however, especially in female patients, a strong inverse relationship between physical activity level and fat mass was observed [14]. The difference between this previous study and the present one is that in the latter, the time of measurement was only between 3 and 6 months after transplantation. It can be hypothesized that early after transplantation, a period in which most patients are inactive, corticosteroids lead to an increase in fat mass which is maintained in patients with reduced physical activity. Later after RTx, the effects of physical activity on body composition might become the predominant factor influencing body composition in RTx patients. The results of the present study with regard to body composition should, however, be interpreted with some caution because the differences did not formally reach significance due to wide variation. Moreover, DEXA cannot be considered a gold standard method, although at present it is assumed to be the most reliable method currently available with regard to body composition in RTx patients [6, 13].

With respect to BMD, the results are more straightforward. The decrease in BMD was significantly higher in patients on corticosteroid treatment than in the group receiving steroid-free immunosuppression. The effect was most pronounced in the vertebral region, which was to be expected, since trabecular bone in the cortical edge of the vertebrae is more susceptible to negative effects of corticosteroids than corticol bone from the hip [1, 5, 11]. Our data are in agreement with several previous studies that showed a significant relationship between steroid treatment and bone loss [3, 9, 11, 17] and with the study by Aroldi et al. [2], in which lumbar BMD increased significantly in patients on cyclosporine monotherapy and decreased significantly in patients receiving combined therapy with corticosteroids and cyclosporine. To our knowledge, the study by Aroldi and the present one are the only prospective data with regard to the effect of steroid withdrawal on BMD in RTx patients.

In the present study, BMD was assessed by DEXA. Although DEXA is as yet by far the most widely used technique for this purpose (despite ongoing discussion regarding the relation between DEXA measurements and fracture risk), it also cannot be considered a gold standard for the assessment of osteoporosis [4]. Vertebral height loss due to osteoporosis might give false elevated levels of BMD. In the present study, however, no significant height loss of the patients (which would give indirect evidence for vertebral height loss) was observed in the short follow-up period after RTx. Moreover, hyperparathyroidism might also have an effect on the DEXA

measurements [1, 3, 11]. However, no difference in parathyroid hormone or calcium levels was observed between patients on steroid immunosuppression and the steroid-free group.

Several caveats from the present study should be mentioned. First, the patient group was rather small and the follow-up rather short. However, it is likely that the effects on BMD and body composition are most pronounced especially early after RTx with relatively high steroid doses. Second, patients were randomized to triple therapy, tacrolimus plus steroids, and tacrolimus plus MMF (steroid-free). For reasons of power, the first two groups were combined. It is well known that MMF frequently causes abdominal side effects such as pain, dyspepsia, and diarrhea and that the use of MMF might, therefore, influence body composition. Indeed, some of the patients participating in the multi-center trial, receiving 1 g MMF/day, had serious abdominal complaints, possibly due to the use of MMF; however, these patients were not included in the present study. Moreover, the changes in body composition between month 3 and month 6 after RTx were not significantly different between the subgroups steroid+/MMF+ and steroid+/MMF− (see Table 2). Interestingly, BMD appeared to decrease to a larger degree in patients in the steroid+/MMF− group than in those in the steroid+/MMF+ group (Table 2); the reason for this is not clear and might be due to chance alone, as no theoretical background for a potential positive effect of MMF on BMD appears to be present. Therefore, although no study has yet investigated the effects of MMF on body composition or BMD, it is not likely that the combination of the subgroups steroid+/MMF+ and steroid+/MMF− into the steroid+ group will have had an important effect on the results of the study.

In conclusion, the increase in body fat percentage in the early phase after RTx tends to be higher in RTx patients randomized to continue steroids than in those randomized to be withdrawn from steroids. However, the effect of early steroid withdrawal on body composition after RTx generally seems to be modest. Early steroid withdrawal appears to have beneficial effects on BMD in RTx patients, especially in the lumbar region.

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