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ORIGINAL ARTICLE

A study on strategies for improving growth and body composition after renal transplantation

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Abstract Allograft function and metabolic effects of four treatment regimens, namely, methylprednisone (MP) standard dose (MP-STD), deflazacort (DFZ), MP-late steroid withdrawal (MP-LSW), and MP-very low dose (MP-VLD), were evaluated in prepubertal patients. MP was decreased by month 4 post-transplantation to 0.2 mg/kg/day in MP-STD and DFZ patients and to <0.1 mg/kg/day in MP-LSW and MP-VLD patients. Starting in month 16 post-transplant, MP was switched to DFZ in the DFZ group and totally withdrawn in the MP-LSW group. Creatinine clearance diminished in the MP-STD and MP-LSW groups from 77±6 to 63±6 ml/min/1.73 $m^2$and from 103±5 to 78±3 ml/min/1.73 m^2, respectively ($p<0.01$ and $p<0.001$, respectively). Height increased >0.5 SDS only in the MP-LSW and MP-VLD groups. The body mass index and fat body mass for height-age increased only in the MP-STD patients ($p<0.05$ and $p<0.01$, respectively). Fat body mass decreased in the DFZ group ($p<0.05$), total cholesterol and LDL-cholesterol increased in the MP-STD group, while LDL-cholesterol and total cholesterol/HDL-cholesterol ratio decreased in the DFZ group ($p<0.01$). Lumbar spine bone mineral density (BMD) for height-age showed an increase in the MP-LSW and MP-VLD groups ($p<0.01$). Our data suggest that MP-LSW and MP-VLD strategies improve linear growth, BMD, the peripheral distribution of fat, and preservation of the bone–muscle unit and maintain the normal lipid profile. The MP-LSW patients had a concerning rate of acute rejections and graft function deterioration in prepubertal patients.

Keywords Body growth · Bone mineral density · Cyclosporin · Deflazacort · Dyslipoproteinemia · Methylprednisone · Renal transplantation · Tacrolimus

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Introduction

Within the context of renal transplantation, strategies to improve body composition, longitudinal growth and the lipid profile should be based on maintaining an excellent allograft function with an optimal immunosuppression. This can be achieved by developing strategies to eliminate

or decrease the side effects of immunosuppressants. Despite their side effects (linear growth failure, obesity, dislipoproteinemia and bone loss, among others), glucocorticoids are the cornerstone of immunosuppression in pediatric renal transplantation.

Glucocorticoid toxicity can be treated by reducing, withdrawing, or withholding steroids. However, this strategy may increase the incidence of acute or chronic allograft rejection and graft loss [1]. Moreover, since the required glucocorticoid dose to achieve optimal immunosuppression is unknown, glucocorticoid dosing and subsequent tapering is performed empirically.

Recent studies show that early or late withdrawal [2–5] or complete avoidance [6, 7] of glucocorticoids right from the beginning of the transplant is associated with an increase in height growth. In line with these observations, we have previously and prospectively demonstrated that (1) methylprednisone (MP)-late withdrawal (>12 months post-transplant) and MP-very low dose (<0.1 mg/kg/day) have similar increments on height growth [8] and (2) deflazacort (DFZ, an oxazoline analog of prednisone) is associated with a lower incidence of side effects than immunosuppressive regimens based upon MP at standard doses (0.2 mg/kg/day) [9]. Finally, to the best of our knowledge, there have been no studies comparing MP-standard dose, DFZ, MP-late withdrawal, and MP-very low dose, and their potential side effects, on pediatric renal transplantation. Therefore, the aim of this study was to evaluate and compare retrospectively the effects of four different glucocorticoid therapeutic strategies on kidney function, linear growth, body composition, lipid profile, and bone mass in prepubertal patients after kidney transplantation.

Patients and methods

All prepubertal patients who regularly attended the Pediatric Renal Transplant section of Hospital Italiano, Buenos Aires, Argentina were considered eligible for our study if they met the following inclusion criteria: (1) had received a kidney from a living-related donor, (2) were prepubertal, (3) had panel reactive antibodies levels <10%, (4) had started a post-transplant immunosuppressive protocol with either cyclosporin microemulsion (CsA) or tacrolimus (Tac), in both cases associated with mycophenolate mofetil (MMF) and glucocorticoids, (5) had a functional allograft beyond the third year after kidney transplantation, (6) had no previous episode of acute or chronic rejection, CsA or Tac toxicity, or renal artery stenosis, (7) had no family history of hyperlipidemia, and (8) had no clinical history of lipid-lowering pharmacological therapy. From a total of 450 patients who underwent consecutive kidney transplantation, 32 fulfilled the criteria for further review of their medical charts/records, and all had been transplanted between 1998 and 2005. All patients were monitored at monthly intervals by routine clinical visits on an outpatient basis. In this study, the analyses on height, weight, lipid profile, bone, fat and lean mass, and allograft function over a 40-month period were performed at three different time-points: month 16 (baseline), month 28 (time 1), and month 40 (time 2) after transplantation. The analysis of the results was performed retrospectively, and the study was approved by the local Ethic Committee.

Immunosuppressive regimens

Patients were divided into four groups according to their steroid therapy: group 1, MP-standard dose (MP-STD); group 2, DFZ (Fig. 1); group 3, MP-late steroid withdrawal (MP-LSW); group 4, MP-very low dose (MP-VLD) (Fig. 2).

The MP-STD and DFZ groups were treated with CsA, starting with an oral dose of 10 mg/kg/day. The whole-blood trough concentration was 250–350 ng/mL (FPIA in AXSYM system; Abbot, Abbott Park, IL) during the first 3 months post-transplantation and was regularly adjusted to maintain therapeutic whole-blood levels between 100–200 ng/ml. The MP-LSW and MP-VLD groups were treated with Tac, starting with 0.1–0.15 mg/kg/day in two divided doses per day, with subsequent adjustments to maintain therapeutic whole-blood levels from 5 to 10 ng/mL (IMx, Abbott). All patients were treated with MMF at daily doses of either 1200 mg/m^2 divided in two doses for patients receiving CsA or 600 mg/m^2 in two divided doses for patients receiving Tac. All patients on Tac were also treated with anti-CD25 [daclizumab, 1 mg/kg/dose (five doses)] as induction therapy.

All patients received intravenous MP 4 mg/kg/day during the first three post-operative days, followed by tapering of the MP from 0.5 to 0.2 mg/kg day by postoperative month 4 in CsA-treated patients (MP-STD and DFZ groups) and to <0.1 mg/kg/day in Tac-treated patients (MP-LSW and MP-VLD groups). Thereafter, from month 4 onwards, patients in the MP-STD group were maintained at 0.2 mg/kg/day until the end of the study. Patients in the DFZ group were maintained on MP at 0.2 mg/kg/day for one additional year and then (month 16) switched to DFZ at equivalent doses (0.3 mg/kg/day) [7]. In the MP-LSW group, from month 4 onwards, patients were maintained on MP at <0.1 mg/kg/day for 1 additional year, with the MP finally withdrawn by month 16. In comparison, patients in the MP-VLD group were maintained at <0.1 mg/kg/day throughout the study protocol.

Clinical and laboratory studies

Weight and height were evaluated as described previously [10] by the same trained observers at 6-month intervals. Body mass index (BMI, defined as weight/height^2) was

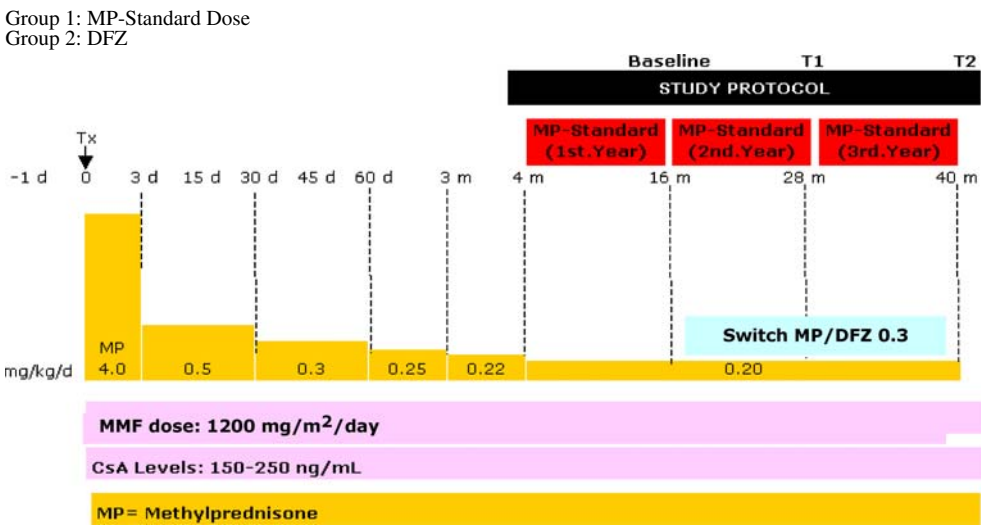

Fig. 1 Immunosuppression regimens in the methylprednisone (*MP*)-standard dose (MP-STD) and deflazacort (*DFZ*) groups. The only difference between the groups was the switch from MP to DFZ from month 16 onwards in the DFZ group. *MMF* Mycophenolate mofetil, *CsA* cyclosporin microemulsion, *Tx* transplantation

assessed using local standards. Office blood pressure within the hypertension range was defined when, at a minimum of three different out-patient visits, the mean of the three systolic and/or diastolic blood pressure readings exceeded the 95th age-matched, sex-matched, and height-matched percentile of adapted reference standard [11]. The stage of puberty was assessed by Tanner's method [12].

Laboratory studies were performed at monthly intervals. Fasting serum concentrations of creatinine, total cholesterol, and triglycerides were measured using standard techniques. High-density lipoprotein (HDL), low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) cholesterol concentrations were calculated with the Friedewald formula [13]. Estimated glomerular filtration rate was calculated for each patient using the modified Schwartz formula [14]. Insulin-like growth factor I (IGF-I) and IGF-binding protein-3 (IGFBP-3) were measured as reported previously [15].

Bone mass was assessed by dual-energy x-ray absorptiometry (DEXA) of the lumbar spine (L2–L4) and total body (Lunar, DPXL/PED; Lunar Radiation Corp, Madison, WI). Measurements at the lumbar spine mainly provide information on trabecular bone. Total skeleton and lumbar mineral density (BMD), bone mineral content (BMC), and total lean and fat mass were calculated by Lunar Software ver. 1.5g (GE Healthcare, Chalfont St. Giles, UK). The coefficient of variation was less than 1.5%. Formulas for total lean and fat mass calculation by the DEXA software are derived from normal children and may not be reliable when applied to children with chronic diseases. For these reasons, results (except height) were expressed as the standard deviation score (SDS), adjusted for "height-age" (age at which a child is at the 50th percentile for height), using local reference data [16]. The regional distribution of body composition was assessed using the ratio of trunk fat percentage over leg fat percentage [17]. We chose this index because 80% of trunk fat mass is perivisceral and 98% of the leg fat mass is subcutaneous. The trunk/leg fat ratio in normal prepubertal children was 0.51±0.1 [mean ±

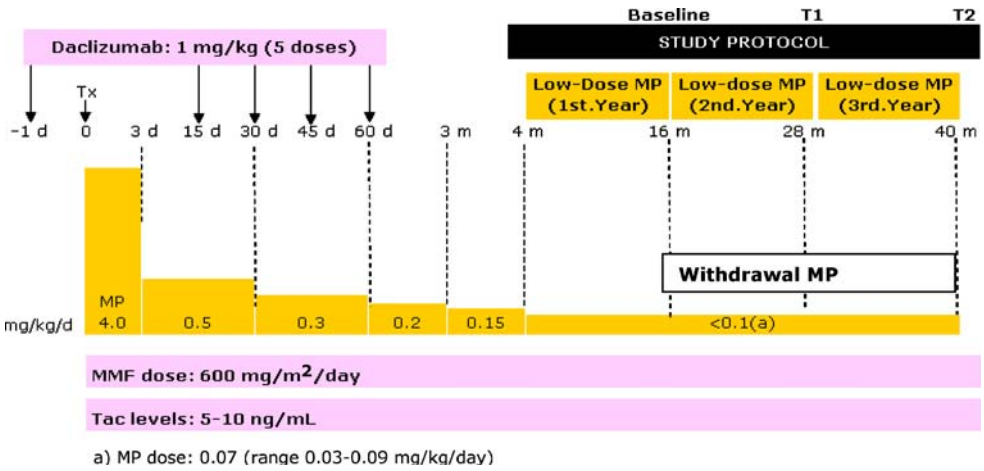

Fig. 2 Immunosuppressive regimens in the MP-late steroid withdrawal (MP-LSW) and MP-very low dose (MP-VLD) groups. The only difference between the groups was that MP was withdrawn from the immunosupression regimen from month 16 onwards in the MP-LSW group. *Tac* Tacrolimus

standard deviation (SD)], and this ratio was expressed as SDS. These measurements were performed at the start of the study (month 16, baseline) and each year afterwards.

Statistical analysis

The significance of differences among treatment groups between baseline (month 16) and year 1 (month 28) and year 2 (month 40) were evaluated by two-way analysis of variance (ANOVA). The post hoc test (Bonferroni) was applied in the case of significant differences among groups. Statistical evaluation of the data was performed using commercially available GraphPad Prism ver. 4.0 (GraphPad Software, San Diego, CA). The results were also analyzed by linear regression, as appropriate. Values are expressed as mean ± standard error (SE), and $p<0.05$ was considered to be statistically significant.

Results

Baseline characteristics of the four patient groups are shown in Table 1. None of the features evaluated were statistically different among the groups. Patients and graft survival at 40 months was 100% in all four groups.

Renal function

The two-way ANOVA analysis revealed a significant difference for interaction, time, and treatment on serum creatinine and creatinine clearance. Treatments did not show the same effects at all time-points (Fig. 3a, b), with serum creatinine levels increasing significantly over time in the MP-STD, DFZ, and MP-LSW groups, but not in the MP-VLD group, and creatinine clearance diminishing significantly over time with the MP-STD and MP-LSW treatments, but showing no reduction with the DFZ and MP-VLD treatments. After 12 and 14 months of MP withdrawal, two patients (22%) developed an acute rejection episode (diagnosed by biopsy), although after MP pulse therapy, creatinine clearance returned to baseline levels.

The frequency of arterial hypertension was not significantly different among and within groups. The percentage of patients in each group with hypertension at month 40 was: MP-STD, 62%; DFZ, 50%; MP-LSW, 44.5%; MP-VLD, 43%. The number of antihypertensive medications was equal among groups (one medication for each hypertensive patient).

Height growth and growth factors

Two-way ANOVA revealed a significant interaction (defined as the appearance of opposite effects during treatment time in the different groups) ($p<0.0001$) among treatment groups and time on height SDS for chronological age. Post hoc testing revealed that while a significant increase in height SDS was observed in the MP-VLD and MP-LSW groups at months 28 and 40, height SDS decreased significantly with MP-STD therapy at month 40 (Fig. 4a). The analysis also revealed a significant difference in height

Table 1 Clinical characteristics of the patients

Patient characteristics	Patient groups according to steroid therapy[a]				*p*
	Group 1: MP-STD	Group 2: DFZ	Group 3: MP-LSW	Group 4: MP-VLD	
Total number of patients (*n*)	8	8	9	7	NS
Male/female (*n*)	5/3	6/2	5/4	3/4	NS
Etiology of ESRD (*n*)					
Dysplasia/uropathy	3	3	4	4	NS
Glomerulopathy	4	4	4	2	NS
Other causes	1	1	1	1	NS
Age at transplant (years)	7.4±0.9 (range 3.9–11)	7.3±1.0 (range 2.9–11.5)	8.2±1.3 (range 3.8–12.0)	7.0±1.0 (range 3.0–11.5)	NS
Age at initiation of protocol (years)	8.4±0.8 (range 5–12)	8.0±0.9 (range 5–12)	9.0±1.3 (range 4.8–13.5)	8.1±1.0 (range 5–13)	NS
Donor age (years, range)	30–45	27–47	34–50	29–49	NS
HLA mismatch					
AB mismatch	1.4±0.2	1.6±0.4	1.5±0.2	1.5±0.2	NS
DR mismatch	0.5±0.2	0.5±0.5	0.5±0.5	0.5±0.5	NS
Follow-up since transplantation (years)	>3.5	>3.5	>3.5	>3.5	NS

MP, Methylprednisone; ESRD, end-stage renal disease; HLA, human leukocyte antigen; NS, not significant

[a] MP-STD, MP-standard dose; DFZ, deflazacort; MP-LSW, MP-late steroid withdrawal; MP-VLD, MP-very low dose

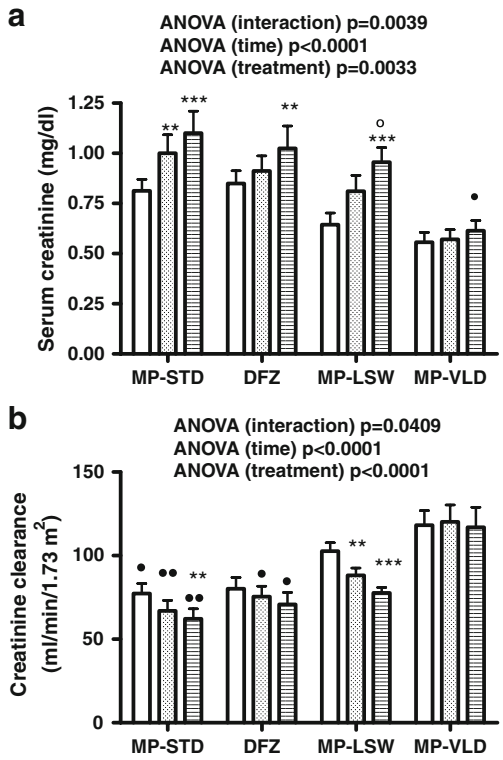

Fig. 3 Serum creatinine (**a**) and creatinine clearance (**b**) over time in patients receiving the MP-STD, DFZ, MP-LSW, and MP-VLD treatments. Comparisons between baseline and each point in time: $^{**}p<0.01$, $^{***}p<0.001$. Comparisons between MP-STD or DFZ vs. MP-VLD: *single solid circle* $p<0.05$, *double solid circle* $p<0.01$. Comparison between month 28 and month 40: *open circle* $p<0.05$. *Open columns* Month 16 (baseline), *columns with dots* month 28, *columns with horizontal lines* month 40

velocity (Fig. 4b) for time ($p=0.0014$) and treatment groups ($p=0.002$). At baseline (16 months), patients on MP initially but then switched to DFZ grew significantly slower than those on MP-LSW and MP-VLD; at month 40, patients on MP-STD grew less than those on MP-LSW (Fig. 4b).

The IGF-I/IGFBP-3 molar ratio SDS for chronological age [18, 19] was significantly different ($p<0.01$) at month 28 between patients treated with MP-STD (−1.8±0.3) or DFZ (−1.8±0.4) versus those treated with MP-LSW (0.11±0.01) or MP-VLD (0.12±0.01).

Body mass index and body composition

The BMI-SDS for height-age was not significantly different among groups. However, a significant BMI-SDS increase ($p<0.05$) was observed at month 40 in patients on MP-STD therapy (Fig. 5a).

Two-way ANOVA revealed a significant interaction ($p=0.0074$) among treatment groups and time on fat body mass-SDS for height age (Fig. 5b). Post hoc testing revealed that while a significant decrease in fat body mass-SDS was observed only in the DFZ group at month 40 versus baseline values, patients treated with MP-STD showed an increase in fat body mass.

The analysis revealed a significant interaction among treatment groups and time in terms of regional distribution of fat, expressed as SDS (Fig. 5c). A significant decrease in this ratio was observed in the MP-LSW group over time.

Lean body mass SDS for height-age was not significantly different among groups throughout the study protocol (Fig. 5d).

Lipid profile

Two-way ANOVA revealed a significant effect of time ($p=0.0232$), treatments ($p<0.001$), and interaction ($p=0.0110$) among treatment groups on total cholesterol (Fig. 6a). Post hoc testing revealed that the MP-LSW strategy produced significantly lower levels of total cholesterol at both month 28 and 40 ($p<0.05$ and $p<0.01$, respectively) than MP-STD therapy. Also at month 40, the MP-VLD group had lower values of total cholesterol than the MP-STD group ($p<0.05$).

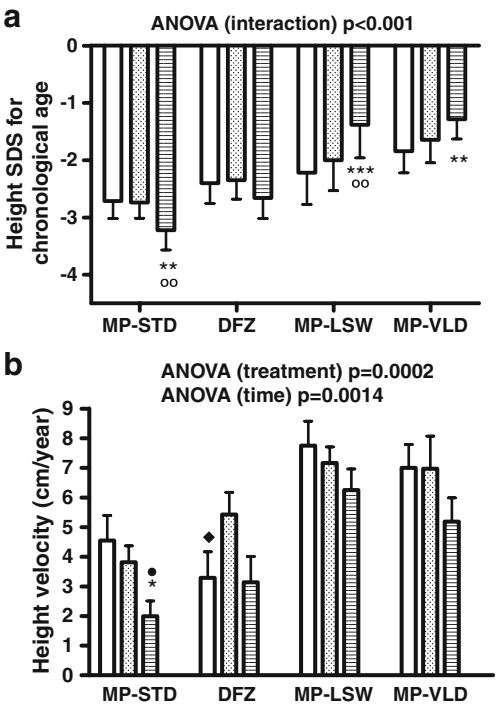

Fig. 4 Height standard deviation score (SDS) (**a**) and height velocity (**b**) in patients receiving MP-STD, DFZ, MP-LSW, and MP-VLD treatments over time. Comparison between baseline and each point in time: $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$. Comparison between month 28 and month 40: *open circles* $p<0.01$. Comparisons between MP-STD vs. MP-LSW: *solid circle* $p<0.05$. Comparison between DFZ vs. MP-LSW and MP-VLD: *solid diamond* $p<0.01$. *Open columns* Month 16 (baseline), *columns with dots* month 28, *columns with horizontal lines* month 40

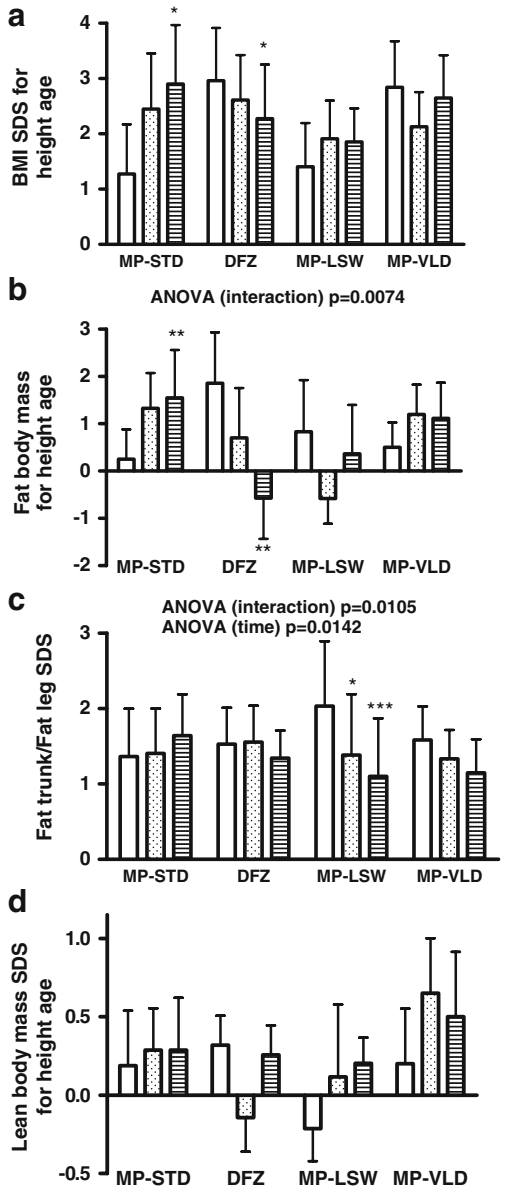

Fig. 5 Body mass index SDS (**a**), fat body mass SDS (**b**), fat trunk percentage/fat leg percentage SDS for prepubertal patients (**c**), lean body mass SDS (**d**) over time in patients receiving the MP-STD, DFZ, MP-LSW and MP-VLD treatments. Comparisons between baseline and each point in time: *$p<0.05$, **$p<0.01$, ***$p<0.001$. *Open columns* Month 16 (baseline), *columns with dots* month 28, *columns with horizontal lines* month 40

The two-way ANOVA analysis revealed a significant effect of time ($p=0.0358$) and treatment ($p=0.0046$) among treatment groups on HDL-cholesterol (Fig. 6b). Post hoc testing revealed that HDL-cholesterol increased significantly ($p<0.05$) over time only with DFZ treatment. At month 40, the patients on MP-LSW therapy showed significantly lower values than those on MP-STD.

The total cholesterol/HDL-cholesterol ratio decreased significantly ($p<0.05$) in the DFZ group at months 28 and 40 (Fig. 6c).

We also observed a significant effect of treatment ($p=0.0019$) and interaction ($p=0.0009$) among treatment groups on LDL-cholesterol (Fig. 6d). Treatments did not show the same effects at all time-points. LDL-cholesterol increased at months 28 and 40 ($p<0.01$ and $p<0.05$, respectively) with MP-STD therapy and decreased at month 28 with DFZ therapy ($p<0.05$). The MP-VLD group showed significantly lower values ($p<0.05$) than the MP-STD group at month 40. The VLDL-cholesterol values showed no change over time in all four groups (data not shown).

Finally, a significant effect of treatment ($p=0.0458$) among treatment groups on serum triglycerides was observed (Fig. 6f), with the best results found in the MP-VLD and MP-LSW groups.

Bone mineral density and content

The two-way ANOVA showed a significant effect of treatment ($p=0.0003$) and interaction ($p = 0.0360$) among treatment groups on lumbar spine-SDS for height-age (Fig. 7a). Post hoc testing revealed that lumbar spine-SDS increased significantly only in the MP-VLD group ($p< 0.05$) at months 16 and 40, compared to the baseline values. The values at month 28 were higher with the MP-VLD therapy than with the MP-STD therapy. At month 40, the lumbar spine-SDS in both the MP-VLD and MP-LSW groups was higher ($p<0.01$ and $p<0.05$, respectively) than that of the MP-STD group (Fig. 7a).

Neither total skeleton BMD nor BMC-SDS for height-age significantly changed over time nor were any differences in any of these parameters found among groups (Fig. 7b, c). However, we found a significant correlation between BMC and lean body mass in all groups of patients ($r=0.83$ for MP-STD, $r=0.88$ for DFZ, $r=0.95$ for MP-LSW, $r=0.94$ for MP-VLD). Moreover, a better correlation was found in both the MP-LSW and MP-VLD groups than in the MP-STD group ($p<0.05$).

Discussion

Previous reports from our group showed that in prepubertal renal transplant patients treated with MP-azathioprine, adequate linear growth was closely related to an excellent allograft function (serum creatinine <1.0 mg/dl) and with the standard dose of MP (0.2 mg/kg/day). However, linear growth remained appropriate only during the first 2 years post-transplantation [20]. When we compared the evolution of the height SDS for chronological age over time for liver and renal transplant patients, liver transplant patients had a better height SDS at transplantation and then showed an adequate catch-up growth, while height SDS did not

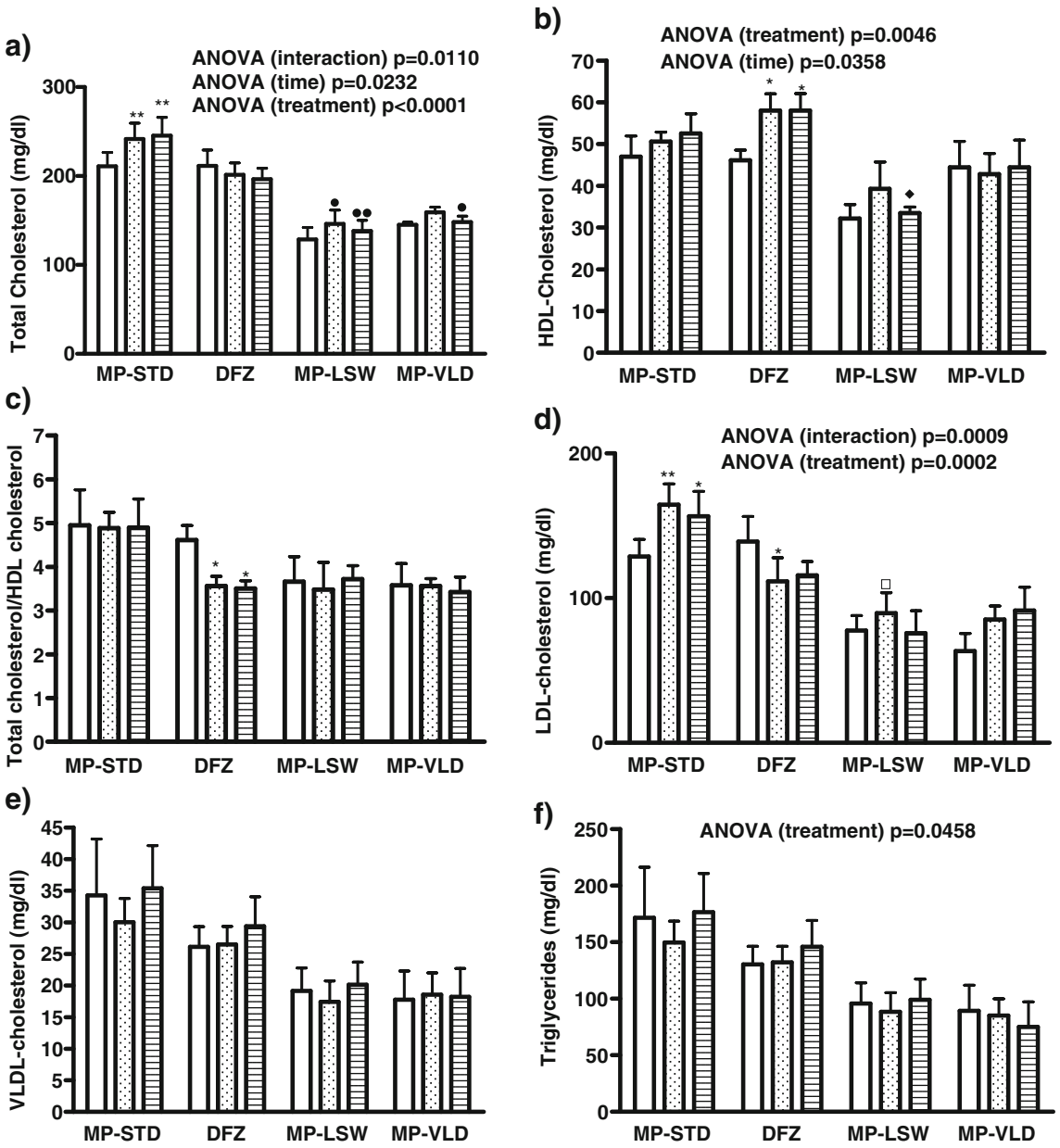

Fig. 6 Total cholesterol (**a**), high-density lipoprotein (*HDL*)-cholesterol (**b**), total cholesterol/HDL-cholesterol ratio (**c**), low-density lipoprotein (*LDL*)-cholesterol (**d**), very low density lipoprotein (*VLDL*)-cholesterol (**e**), and triglycerides (**f**) levels over time in patients receiving the MP-STD, DFZ, MP-LSW, and MP-VLD treatments. Comparisons between baseline and each point in time: *$p<0.05$, **$p<0.01$. Comparisons between MP-VLD and MP-LSW vs. MP-STD: *solid circle* $p<0.05$, *two solid circles* $p<0.01$. Comparison between MP-LSW vs. DFZ: *solid diamond* $p<0.05$. Comparison between MP-LSW vs. MP-STD: *open square* $p<0.05$. Normal values of the lipid profile are: total cholesterol ≤200 mg/dl (**a**), HDL-cholesterol ≥40 mg/dl (**b**), total cholesterol/HDL-cholesterol ratio ≤4.5 (**c**), LDL-cholesterol ≤100 mg/dl (**d**), VLDL- cholesterol ≤30 mg/dl (**e**), triglycerides ≤150 mg/dl (**f**). *Open columns* Month 16 (baseline), *columns with dots* month 28, *columns with horizontal lines* month 40

improve after renal transplantation. It was originally believed that these discrepancies were due to: (1) reduced renal graft function in renal transplant patients, (2) growth factors (IGF-I, IGFBP-3 and their molar ratio) reaching normal values in liver transplant patients but not in renal transplant patients, and (3) the reduction and discontinuation of immunosuppressive corticoid dosage in liver transplant patients [21]. At that time, we believed it would be a challenge to modify steroid therapy without altering graft function in children with renal transplants.

In a previous study, we showed that the conversion from MP to DFZ, an steroid with fewer side effects, prevents height loss, excessive bone loss, and fat accumulation and improves the lipoprotein profile in prepubertal patients after

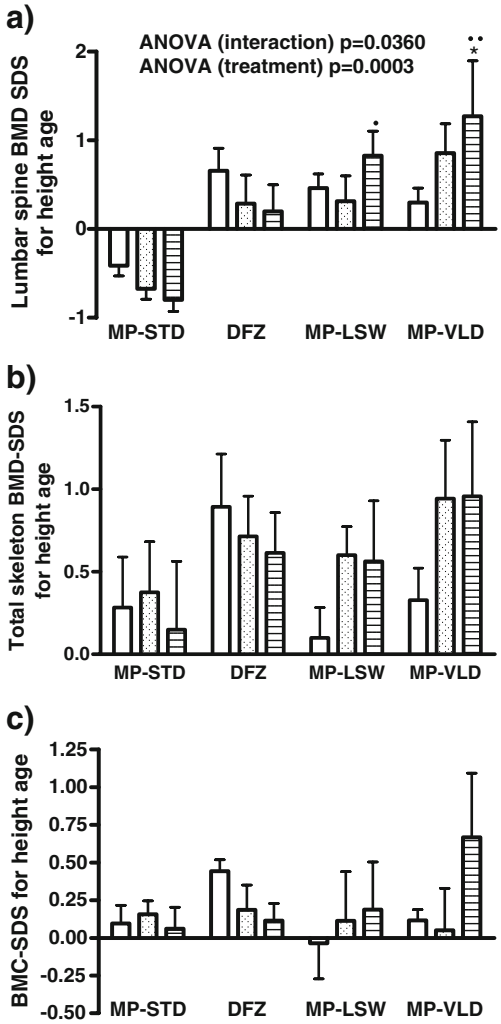

Fig. 7 Lumbar spine bone mineral density (*BMD*)-SDS (**a**), total skeleton BMD-SDS (**b**), and bone mineral content (*BMC*)-SDS (**c**) over time in patients receiving MP-STD, DFZ, MP-LSW, and MP-VLD treatments. Comparisons between baseline and each point in time: *$p<0.05$. Comparisons between MP-VLD and MP-LSW vs. MP-STD: *sold circle* $p<0.05$, *two solid circles* $p<0.01$. *Open columns* Month 16 (baseline), *columns with dots* month 28, *columns with horizontal lines* month 40

renal transplantation [9]. We also demonstrated that a reduced dose of MP versus MP withdrawal allowed excellent catch-up growth and resulted in both a normal lipid profile and a normal bone mineral mass [8].

Steroids are always associated with a calcineurin inhibitor. In this respect, we [22, 23] and other researchers [24, 25] have shown that Tac- and MMF-based immunosuppression is related to better allograft function and protection against allograft deterioration than CsA or azathioprine immunosuppressive regimens. Therefore, the better renal function observed in both our MP-VLD and MP-LSW groups (both on Tac and MMF) at month 16 was an expected finding. However, after MP withdrawal, creatinine clearance decreased dramatically in these groups after 1 and 2 years and, moreover, 22% of patients developed acute rejection episodes. These last two observations provide evidence that a very low steroid dose (almost equivalent to the endogenous daily glucocorticoid production rate) exerts immunosuppressive activity. One possible explanation for this activity may be due to the addition of endogenous cortisol production to exogenous steroid therapy as well as the concomitant use of more potent immunosuppressants that may modify steroid receptor number and/or affinity.

Our results may be explained by the fact that glucocorticoids prevent T-cell activation by inhibiting the release of T-cell-derived and antigen-presenting cell-derived cytokines, and these are reversible effects that could rebound if glucocorticoids are withdrawn, thus increasing the risk of rejection [26]. Whereas creatinine and creatinine clearance did not change throughout the study in the MP-VLD group, creatinine clearance decreased significantly in the MP-STD and MP-LSW groups and showed no change after the patients switched from MP to DFZ. This last result may be due to a better immunosuppressive activity of DFZ in pediatric renal transplantation [27].

On the other hand, the first prospective randomized trial on late glucocorticoid withdrawal in prepubertal and pubertal renal recipients receiving CsA and MMF therapy showed no increased risk of acute rejection [28, 29].

Height SDS increased significantly after 2 years of follow-up (range 0.9–0.6 SDS) in patients on MP-LSW and MP-VLD therapy, while MP-STD-treated patients showed a significant fall in height SDS and DFZ-treated patients showed no change at all. These results are in accordance with observed growth velocity changes. Patients on MP-LSW and MP-VLD continued growing at the same height velocity as at baseline (5–7 cm/year); in DFZ-treated patients, however, height velocity increased above baseline (2.5 cm/year) only during the first year, returning almost to baseline levels during the second year of our study. Similar results have been reported previously [9]. In patients treated with MP-STD, height velocity decreased from 5 to 2 cm/year after 2 years. Furthermore, the IGF-I/IGFBP3 molar ratio SDS for chronological age was significantly decreased in the MP-STD and DFZ groups versus the MP-LSW and MP-VLD groups. These favorable hormonal differences together with an adequate renal function may help to explain the improvement in linear growth in patients on MP-VLD and MP-LSW therapy during this study.

An interesting clinical observation was that after 2 years of follow-up, Cushingoid appearance was commonly observed in the MP-STD group but not in DFZ, MP-LSW and MP-VLD groups. The four groups of patients showed different changes in BMI and body composition in terms of SDS for height-age. Correction for height-age is important for monitoring prepubertal children with chronic renal

failure in whom growth delay is common. Height-age evaluates a child's body composition based on size rather than on age [30, 31]. After correcting for height-age, we found that the BMI-SDS was different among the groups, decreasing in DFZ patients but increasing in MP-STD patients. DEXA can be used to estimate lean and fat mass in patients with chronic renal failure and post-transplantation patients. The main concern over the accuracy of DEXA is its failure to measure total body water. This is particularly pertinent to chronic renal failure as in the presence of fluid overload, there can be an overestimation of lean mass; however, this was not the case with our transplant patients. Fat body mass-SDS increased significantly only in the MP-STD-treated patients. As fat body mass-SDS failed to define compartment differences in body composition, we assessed the ratio trunk fat (percentage) over leg fat (percentage). At the end of the study, only patients in the MP-STD group was the mean value for this ratio >1.5 SDS, indicating an increase in the central distribution of fat. Lean body mass was not different among groups throughout the study, with mean values ranging between −0.25 and 0.7 SDS. These changes suggest that the glucocorticoid dose and type play an important role in fat accumulation.

The almost normal BMI and lack of fat accumulation with a lower central distribution of fat in the MP-LSW and MP-VLD groups were associated with normal lipid profile, especially total cholesterol, total cholesterol/HDL-cholesterol ratio, LDL-cholesterol, VLDL-cholesterol, and triglycerides. This normal profile may decrease cardiovascular risk in later life. These advantages were not seen in patients treated with MP-STD, and they were only partially observed in patients after conversion from MP-STD to DFZ therapy. This could be due to the use of CsA instead of Tac, which has been associated with dyslipidemia [22]. Steroids also have an adverse impact on insulin sensitivity and glucose metabolism. Therefore, in our MP-STD-treated patients, the link between the increase in BMI, fat accumulation, and the abnormal lipid profile may rest in a decrease in insulin sensitivity [9].

We found an increase in lumbar spine BMD SDS with a very low dose or after withdrawal of MP. The linear regression analysis showed a positive correlation between lean body mass and BMC.

This study analyzed four different steroid therapy strategies in pediatric renal transplant patients, namely MP-STD and DFZ, both concomitant with CsA and MMF, and MP-LSW, and MP-VLD, both concomitant with TAC and MMF. Patients receiving the MP-LSW and MP-VLD treatments showed better height growth than those treated with MP-STD or DFZ. The BMI-SDS (for height-age) and fat body mass-SDS increased significantly only in the MP-STD-treated patients, while the BMD-SDS (for height-age) improved only in patients on MP-VLD therapy. Both the MP-LSW and MP-VLD groups maintained a normal lipid profile throughout the period of study. Finally, impairment of the allograft function was observed in both the MP-STD and MP-LSW groups, with steroid withdrawal being associated with rejection episodes.

The main limitations of this study were the small number of patients enrolled and the retrospective and single-center design of the study. However, the comparison of the data among and within groups reinforces the validity of the findings.

Conclusion

Post-transplant height changes have a closer relationship with the dose than with the type of steroid. In addition, Tac, MMF, and MP-VLD treatments are associated with excellent height growth, allograft function, lipid profile, and increment in bone mass. A longer follow-up would be necessary to observe if these advantages are maintained over time. Our results support those reported previously [32] suggesting that chronic exposure to steroids in prepubertal patients may produce dependence, making tapering immunologically unsafe. Consequently, late steroid withdrawal is not advisable due to an increased incidence of acute rejection and allograft function impairment, despite the use of anti-interleukin-2, Tac, and MMF. In those patients requiring standard doses of steroids, we suggest that DFZ should be considered in order to reduce the incidence of steroid-induced side effects.

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