Effect of Immunosuppression on Kidney and Serum Insulin-Like Growth Factor-I (IGF-I), IGF Binding Proteins, and Renal Growth Following Unilateral Nephrectomy in Rats

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A rat model was used to study the role of renal insulin-like growth factor-I (IGF-I) and circulating IGF-I and IGF binding proteins (IGFBPs) in early posttransplantation renal hypertrophy and overall body growth during high-dose immunosuppression. Seven days of prednisolone and cyclosporin A (CsA) immunosuppression was administered to rats following unilateral nephrectomy compared with sham-operated controls. Immunosuppression of nephrectomized and control rats was followed by a reduction in body weight (BW) compared with placebo treatment. In addition, immunosuppression inhibited kidney IGF-I accumulation and compensatory renal growth in uninephrectomized rats, but caused no change in kidney weight or IGF-I levels in control rats. Immunosuppression induced a sustained significant increase in circulating IGFBP-3 and 30-kd IGFBPs in uninephrectomized and controls rats, whereas serum IGF-I levels were unchanged. In a supplementary study separating the effects of the two immunosuppressants, the kidney IGF-I changes and renal growth were primarily affected by CsA, while the changes in IGFBPs appeared to be caused by prednisolone treatment. In conclusion, immunosuppression with prednisolone and CsA was followed by less kidney IGF-I accumulation and compensatory renal growth compared with placebo treatment. In addition, a sustained increase in circulating levels of IGFBP-3 and 30-kd IGFBPs was observed, which may be involved in the growth impairment observed following immunosuppressive treatment.

PREDNISOLONE AND CYCLOSPORIN A (CsA) are the prevailing agents used to avoid organ rejection after renal transplantation. Immunosuppression is most intense in the early posttransplantation period, when the renal transplant is particularly vulnerable due to preoperative and postoperative damage and general ill health. In addition, in this early phase the transplanted kidney is exposed to local and humoral factors stimulating hypertrophy, which may further strain the requirements and condition of the renal tissue. Finally, children receiving renal transplant are already stunted in growth and continue to be during the immunosuppressive treatment.

Recent studies of changes in the growth hormone (GH) and insulin-like growth factor-I (IGF-I) axis have suggested adverse effects of immunosuppression. Especially prednisolone induces changes in GH secretion and circulating IGF-I levels, although results have not been consistent.[1-4] However, IGF-I bioactivity has been demonstrated to be clearly reduced,[5,6] and in a previous clinical study, stimulation of circulating IGF binding proteins (IGFBPs) was demonstrated following immunosuppressive treatment.[7]

In the initial posttransplantation phase, the recipient kidney is exposed to uremia, postoperative and prior chronic stress and catabolism, an activated immune defense, and the drastic early immunosuppression. At the same time, the transplanted kidney is challenged by humoral and local factors inducing it to enlarge and to hyperfunction. Previous studies in rats have demonstrated that compensatory renal growth is related to a preceding accumulation of kidney tissue IGF-I.[8,9] In addition, when kidney IGF-I accumulation is abolished by administration of the somatostatin analog octreotide, a potent inhibitor of GH and IGF-I, the early compensatory renal growth is prevented,[9] providing further evidence for IGF-I as a renotropic factor. The effect of immunosuppression on compensatory renal growth has been examined in a few previous studies; however, only CsA treatment was used.[10-12] It was demonstrated that high-dose CsA had inhibitory effects on compensatory renal growth following unilateral nephrectomy, while low-dose CsA[12] had no effect. However, kidney IGF-I changes were not investigated in the previous studies.

The aim of the present study was to investigate the effect of combined treatment with CsA and prednisolone on serum and kidney IGF-I and IGFBPs, compensatory renal growth, and body weight (BW) changes following unilateral nephrectomy in rats compared with sham-operated control rats. Further, in a supplementary study, the effect on the same parameters of either prednisolone or CsA treatment alone was examined separately at the end of a 7-day experimental period in sham-operated controls and nephrectomized rats.

MATERIALS AND METHODS

Animal Protocol

Adult male Wistar rats (Møllegaards Avlslab, Eiby, Denmark) with a mean BW of 217 ± 3 g (n = 78 in study 1 and n = 46 in study 2) were studied. Rats were housed two to three per cage in a room with a 12-hour (6:30 AM to 6:30 PM) artificial light cycle, temperature 21 ± 2°C, and humidity 55% ± 2%. The animals had free access to standard rat chow (Altromin, Lage, Germany) and tap water throughout the experiment. By day 0, rats in study 1 were randomized by weight into the following groups: (1) placebo-treated controls (n = 18), (2) prednisolone and CsA–treated controls (n = 12), (3) uninephrectomized placebo-treated (n = 24), and (4) nephrectomized prednisolone and CsA–treated (n = 24). In study 2, rats were randomized by weight into the following groups: (1) placebo-treated controls (n = 6), (2) CsA-treated controls (n = 8), (3) prednisolone-treated controls (n = 8), (4) placebo-treated uninephrectomized (n = 8), (5) CsA-treated uninephrectomized (n = 8), and (6) prednisolone-treated uninephrectomized (n = 8). Right kidney uninephrectomy or sham operation was performed by day 0 under barbital anesthesia (50 mg/kg BW intraperitoneally [IP]). The right kidney was exteriorized, decapsulated, and removed through a flank incision in unilaterally nephrectomized rats, whereas it was replaced in

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the abdomen in sham-operated control rats. Immunosuppression with prednisolone (Delcortol; Løvens Kemiske Fabrik, Ballerup, Denmark) 4 mg/kg BW and CsA (Sandimun; Sandoz, Basel, Switzerland) 10 mg/kg BW was administered as once-daily subcutaneous injections. Placebo-treated animals were injected with 0.5 mL 0.9% NaCl subcutaneously. BW and food intake were measured every day. In study 1, sham-operated control animals were examined at days 0, 4, and 7, six rats per day. Animals subjected to nephrectomy were examined at days 2, 4, and 7, eight rats from each group per day. In study 2, animals from each group were examined at the end of the 7-day study period.

At the end of the experiments, the rats were anesthetized with sodium barbital (50 mg/kg BW IP) and rapidly dissected to obtain the kidney after blood sampling from the retrobulbar venous plexus. The sera and kidneys were rapidly frozen and kept at −80°C until further analysis.

Kidney and Serum IGF-I Measurements

Kidney IGF-I extraction was performed according to the method of D'Ercole et al,[13] and serum IGF-I was extracted using acid-ethanol extraction. IGF-I radioimmunoassay was performed as previously described.[14,15] The intraassay coefficient of variation (CV) was 5.4% and the interassay CV 9.3%. However, all samples were analyzed in a single assay.

IGFBPs

Sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) and Western ligand blot analysis of IGFBPs were performed according to the method of Hossenlopp et al[16] as previously described.[17] Sera from one animal from each group were represented on each gel in the two separate studies. Autoradiographs of ligand blots were scanned using a laser densitometer (CS-9001PC; Shimadzu, Kyoto, Japan). The relative densities of the bands were measured as arbitrary absorbency units per square millimeter.

Statistical Analysis

The results are presented as the mean ± SEM. Differences between groups were analyzed by one-way ANOVA in combination with the Duncan test for multiple comparisons or the Kruskall-Wallis test for data not following a normal distribution, followed by the Mann-Whitney test. Statistical analyses were performed with the statistical package SOLO (BMDP Statistical Software, Los Angeles, CA). A P level less than .05 was considered statistically significant in a two-tailed test.

RESULTS

Study 1

BW. BW changes in the four experimental groups are shown in Fig 1. All four groups exhibited a small initial decrease in BW following the anesthesia and surgical procedure. Placebo-treated control and nephrectomized rats exhibited a significant BW gain throughout the remaining experiment, while both groups of rats receiving immunosuppression had no BW gain after the initial decrease. No significant differences in BW were observed between the two placebo-treated or two immunosuppressed groups, respectively. From day 2 and throughout the study period, a significant difference in BW was observed between placebo-treated control rats, nephrectomized rats, and rats receiving immunosuppression ($P < .05$).

Food intake. Food intake in the animals throughout the study period is shown in Fig 2. The combined immunosuppressive treatment was followed by a significant reduction in food intake in nephrectomized and control rats compared with placebo-treated rats ($P < .05$). However, no difference was observed between placebo-treated or between immunosuppressed animals, respectively. When food intake was expressed per unit BW, no significant difference in food intake was observed between any of the experimental groups.

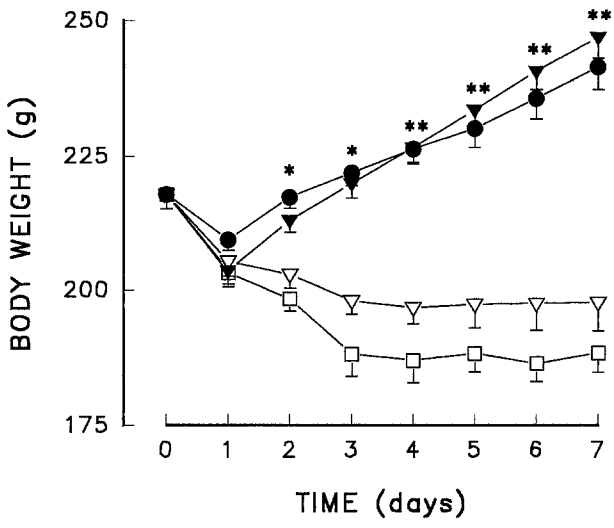


Fig 1. Changes in body weight in placebo-treated control (●), immunosuppressed control (▽), and nephrectomized placebo-treated (▼) and immunosuppressed (□) rats during the 7-day study period. *$P < .05$, nephrectomized placebo-treated *v* immunosuppressed nephrectomized and placebo-treated *v* immunosuppressed control on each day, respectively. **$P < .001$, nephrectomized placebo-treated *v* nephrectomized immunosuppressed rats and placebo-treated controls *v* immunosuppressed controls on days 4, 5, 6, and 7.

Kidney weight. Changes in kidney weight are shown in Fig 3. Both groups of nephrectomized rats exhibited a significant

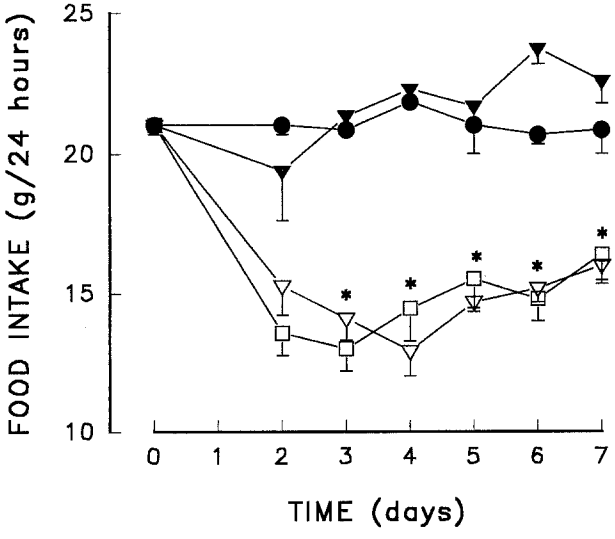


Fig 2. Food intake per 24 hours in placebo-treated controls (●), immunosuppressed control (▽), and nephrectomized placebo-treated (▼) and immunosuppressed (□) rats during the 7-day study period. *$P < .05$, immunosuppressed control or nephrectomized rats *v* placebo-treated nephrectomized and control rats on days 3, 4, 5, 6, and 7.

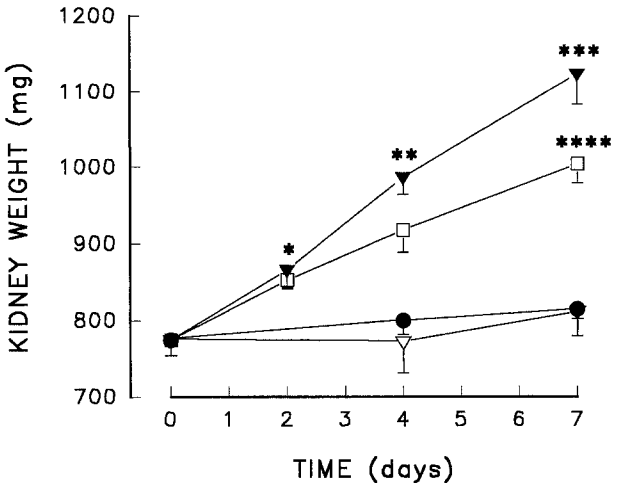


Fig 3. Changes in kidney weight during the experimental period in placebo-treated control (●), immunosuppressed control (▽), and nephrectomized placebo-treated (▼) and immunosuppressed (□) rats during the 7-day study period. *$P < .05$, nephrectomized placebo-treated and immunosuppressed rats day 2 *v* placebo-treated control rats day 0. **$P < .05$, placebo-treated nephrectomized *v* placebo-treated control rats and immunosuppressed nephrectomized *v* immunosuppressed control rats by day 4. ***$P < .05$, placebo-treated nephrectomized *v* placebo-treated controls and immunosuppressed nephrectomized *v* immunosuppressed controls day 7. ****$P < .05$, placebo-treated nephrectomized *v* immunosuppressed nephrectomized day 7.

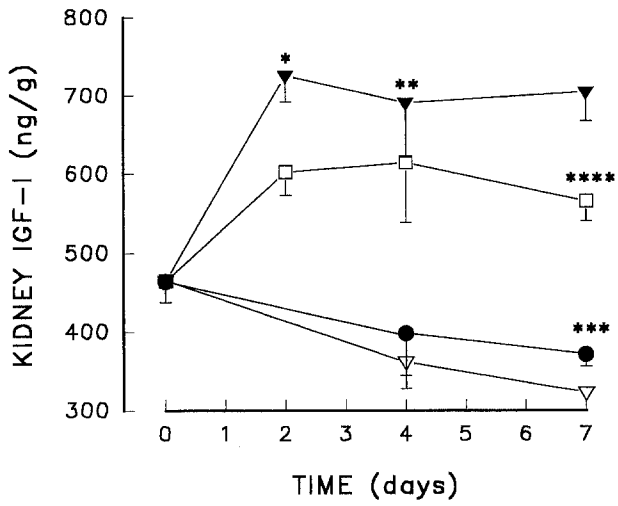


Fig 4. Changes in kidney IGF-I levels in placebo-treated control (●), immunosuppressed control (▽), and nephrectomized placebo (▼) and immunosuppressed (□) rats during the 7-day study period. *$P < .01$, nephrectomized placebo-treated and immunosuppressed nephrectomized day 2 *v* placebo-treated controls day 0. **$P < .05$, placebo-treated nephrectomized *v* placebo-treated control and immunosuppressed nephrectomized *v* immunosuppressed control day 4. ***$P < .01$, placebo-treated control *v* placebo-treated nephrectomized and immunosuppressed control *v* immunosuppressed nephrectomized day 7. ****$P < .01$, nephrectomized immunosuppressed *v* placebo-treated nephrectomized day 7.

increase in kidney weight from day 2 and throughout the experimental period compared with control rats ($P < .05$). The increase in kidney weight was more pronounced in placebo-treated nephrectomized rats compared with immunosuppressed nephrectomized rats, and was statistically significant by the end of the study period ($P < .05$). No difference in kidney weight was observed between sham-operated control rats with or without immunosuppression (NS). With the kidney weight corrected for differences in BW both immunosuppressed groups had significantly higher kidney weight to BW ratios compared with the placebo-treated groups, respectively, during the study period ($P < .05$). Further, immunosuppressed nephrectomized rats had an even higher kidney weight to BW ratio compared with placebo-treated nephrectomized rats ($P < .05$). By day 7, kidney weight to BW ratios were as follows: placebo-treated controls, 338 ± 11 mg/100 g BW; immunosuppressed controls, 410 ± 11; placebo-treated nephrectomized rats, 454 ± 12; and immunosuppressed nephrectomized rats, 533 ± 10.

Kidney IGF-I. Changes in the total kidney IGF-I concentration in the four experimental groups are shown in Fig 4. Both nephrectomized groups exhibited a significant increase in kidney IGF-I levels at day 2 compared with control rats at days 0, 4, and 7 ($P < .05$). In addition, the increase in IGF-I in placebo-treated nephrectomized rats was significantly higher by day 7 ($P < .05$), while only a trend toward higher kidney IGF-I levels was observed by day 2, compared with immunosuppressed nephrectomized animals ($.05 < P < .10$). No difference in kidney IGF-I levels was observed between the two sham-operated control groups.

Serum IGF-I. No major changes in serum IGF-I levels occurred in the four experimental groups (Fig 5).

Serum IGFBPs. Using Western ligand blotting (Fig 6), three bands of serum IGFBPs were observed, and the data expressed as arbitrary units per square millimeter are given in Fig 7A, B, and C. A doublet of 38 to 42 kd representing IGFBP-3 was observed (Fig 7A), followed by a smaller band of 30-kd IGFBPs (corresponding to IGFBP-1 and IGFBP-2; Fig 7B). The third and smallest band had a molecular weight of 24

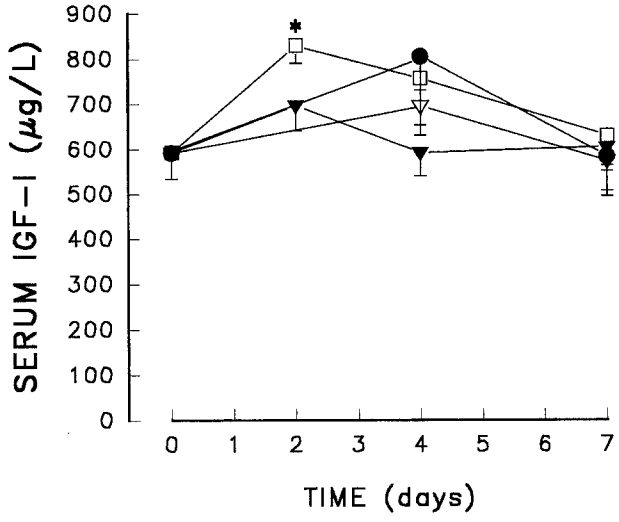


Fig 5. Changes in total serum IGF-I levels during the experimental period in placebo-treated control (●), immunosuppressed control (▽), and nephrectomized placebo-treated (▼) and immunosuppressed nephrectomized (□) rats during the 7-day study period. *$P < .05$, immunosuppressed nephrectomized day 2 *v* placebo-treated control day 0.

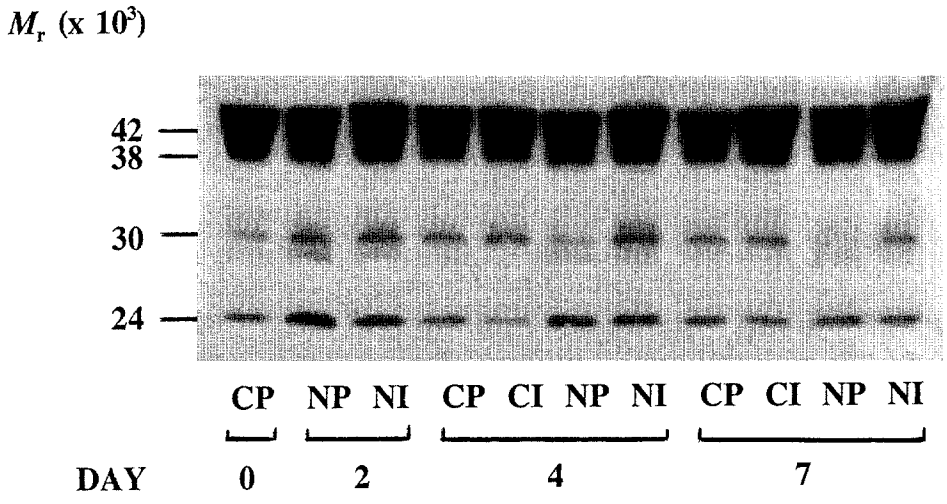


Fig 6. A representative Western ligand blot for sera from rat groups examined on days 0, 2, 4, and 7 in study 1. CP, placebo-treated controls; CI, immunosuppressed controls; NP, nephrectomized placebo-treated rats; NI, nephrectomized immunosuppressed rats. Three bands were observed, ie, a double band of 38 to 42 kd representing IGFBP-3, a 30-kd band representing IGFBP-1 and IGFBP-2, and a 24-kd band representing IGFBP-4.

kd, representing IGFBP-4 (Fig 7C). In both groups receiving immunosuppression, a sustained increase in IGFBP-3 was observed, being significantly different from the values in placebo-treated groups by the end of the study ($P < .05$). A similar pattern was observed in the 30-kd band, with a significant increase by day 2 compared with day 0 in both nephrectomized groups ($P < .05$). In immunosuppressed nephrectomized and control rats, a sustained increase was observed by the end of the study compared with the levels in placebo-treated nephrectomized and control rats ($P < .05$). A significant transient increase in the IGFBP-4 band was observed in placebo-treated uninephrectomized rats by day 2 compared with placebo-treated control rats by day 0, while no differences in IGFBP-4 levels were observed between the four groups by day 4 or day 7.

Study 2

Both prednisolone and CsA treatment were followed by a significant inhibition of BW gain compared with placebo treatment in nephrectomized and control rats by the end of the study period ($P < .05$; Table 1). A decreased food intake was observed in groups treated with CsA or prednisolone compared with the placebo-treated groups ($P < .05$). Unilateral nephrectomy in all three groups was followed by a significant increase in kidney weight compared with the respective control value ($P < .05$). However, CsA-treated nephrectomized rats had a significantly smaller increase in kidney weight compared with placebo and prednisolone treatment ($P < .05$). By day 7, CsA-treated rats had significantly lower kidney IGF-I levels compared with placebo-treated rats ($P < .05$), while prednisolone-treated rats had similar IGF-I levels as placebo-treated controls ($P < .05$). No significant differences in serum IGFBP-3 levels were observed by ANOVA. However, uninephrectomized prednisolone-treated rats had significantly higher IGFBP-3 levels compared with placebo-treated controls ($P < .05$). Prednisolone treatment was followed by a significant increase in the 30-kd IGFBPs (IGFBP-1 and IGFBP-2) compared with placebo treatment ($P < .05$) (Table 1).

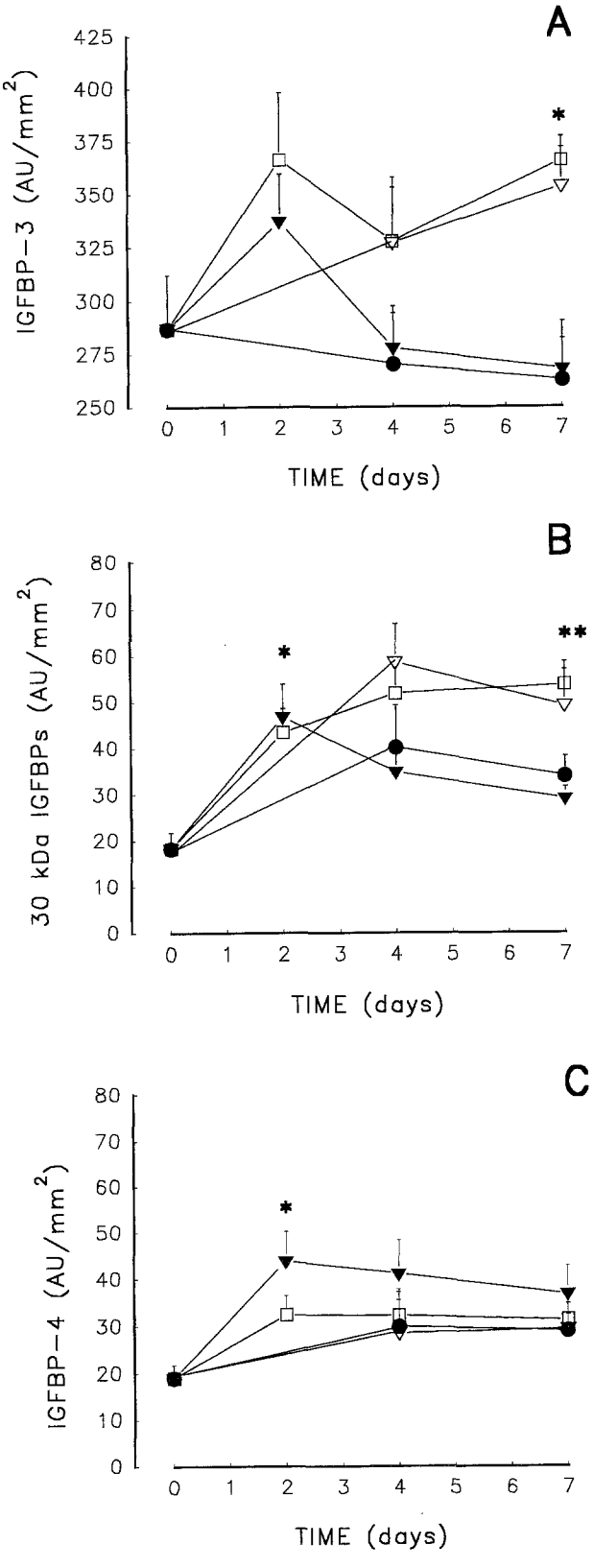
DISCUSSION

Consistent with previous studies, placebo-treated uninephrectomized rats showed a significant increase in the wet weight of the remaining kidney during the 7-day experimental period.[8,18] A transient increase in extractable kidney IGF-I of the remaining kidney has been demonstrated previously, with a maximal level after 24 to 48 hours declining to the baseline level by day 4 following uninephrectomy.[8] However, Evan et al[19] observed an increase in both kidney IGF-I and IGF-I mRNA by day 5 following uninephrectomy, and increased renal IGF-I has been demonstrated even later after uninephrectomy.[19,20] Kidney IGF-I levels were significantly higher than control levels by the end of the 7-day experimental period in both nephrectomized groups (study 1), thus confirming that the transient kidney IGF-I increase following uninephrectomy may last longer than the 2 to 3 days we found originally.[8] In the present study, renal hypertrophy was demonstrated in both groups of nephrectomized animals; however, immunosuppressed rats had a significantly smaller increase in kidney weight compared with placebo-treated rats by the end of the study. In addition, a statistically significant reduction of renal IGF-I accumulation was observed in immunosuppressed nephrectomized rats compared with placebo-treated uninephrectomized rats, showing that immunosuppression indeed influences the renal IGF-I system. The diminished renal IGF-I accumulation in immunosuppressed animals may be involved in the diminished compensatory renal growth as compared with placebo-treated nephrectomized rats. In a recent study from our group, it was demonstrated that kidney IGF-I accumulation correlated positively with the amount of renal tissue resected and the following compensatory renal growth.[18]

In study 2, it was demonstrated that this inhibition of compensatory renal growth was apparently caused by CsA, while prednisolone had no influence on renal hypertrophy compared with placebo treatment in nephrectomized rats. This is in contrast to a previous study using a similar CsA dose,[12] whereas inhibition of compensatory renal growth has been demonstrated using higher doses of CsA.[10,11] However, kidney IGF-I changes were not examined. In addition, by the end of the study period, CsA-treated uninephrectomized rats had significantly lower kidney IGF-I levels compared with placebo- and prednisolone-treated rats, which may suggest that CsA inhibits renal growth partly via reduced IGF-I levels. In addition, CsA-treated control rats had significantly lower kidney IGF-I levels compared with placebo-treated control rats, which pro-

vides further support for an effect of CsA on kidney IGF-I. However, there was no significant difference in kidney weight compared with placebo-treated control rats.

In study 1, a significant inhibition of BW gain was observed in immunosuppressed uninephrectomized and sham-operated control rats, while the BW increase was identical in placebo-treated uninephrectomized and control rats. In study 2, both prednisolone and CsA administration were followed by a similar inhibition of BW gain by the end of the experimental period. It has previously been shown that IGF-I bioactivity following immunosuppression is decreased, which may be caused by significant changes in circulating IGFBPs.



In the present study, combined treatment with CsA and prednisolone resulted in a significant increase in IGFBP-3 levels in study 1. In study 2, this effect seemed to be mediated by prednisolone. However, prednisolone-treated nephrectomized rats only had a significantly higher IGFBP-3 level compared with placebo-treated controls. Previous studies have shown IGFBP-3 levels to be increased during a short-term dexamethasone treatment period along with increased IGF-I levels in healthy subjects while IGF bioactivity was decreased.[21,22] Increased IGFBP-3 levels have also been demonstrated in rats treated with dexamethasone for up to 6 days.[23] The increase in IGFBP-3 levels following steroid treatment in man seems not to be caused by increased GH secretion, which, on the contrary, is decreased in states of steroid excess[24]; however, a second study demonstrated an increase in daytime GH secretion but a delayed and attenuated effect on nocturnal GH pulses.[25]

Circulating IGFBP-1 levels are primarily regulated by metabolic factors, with insulin as the major physiologic determinant.[26,27] It has therefore been suggested that corticosteroids regulate IGFBP-1 levels via changes in insulin levels. However, in previous studies, it has been demonstrated that corticosteroids independent of insulin regulate IGFBP-1 levels in vitro[28] and in vivo.[29,30] Thus, Conover et al[31] demonstrated that cortisol itself stimulated IGFBP-1 levels in healthy humans during a euglycemic pancreatic clamp. In none of the presented studies were significant differences in prevailing serum insulin levels demonstrated between any of the experimental groups (data not shown), and especially, no effect of prednisolone treatment was observed. This may reflect that the blood was drawn from nonfasted animals, which may disturb the comparison of insulin levels. However, it may also support the notion that corticosteroids stimulate circulating IGFBP-1 (and IGFBP-2) levels directly.

It may be suggested that the observed changes in IGFBPs may be partly involved in the growth retardation observed in immunosuppressed animals and primarily mediated by prednisolone. The increased levels of IGFBP-3 and 30-kd IGFBPs may decrease the biologically active fraction of serum IGF-I, leading

Fig 7. Changes in serum IGFBPs during the experimental period in placebo-treated control (●), immunosuppressed control (▽), and nephrectomized placebo-treated (▼) and nephrectomized immunosuppressed (□) rats during the study period. (A) Changes in serum IGFBP-3 levels. *$P < .05$, immunosuppressed nephrectomized and control rats *v* placebo-treated nephrectomized and control rats, respectively, day 7. (B) Changes in 30-kDa IGFBP (IGFBP-1 and IGFBP-2) levels. *$P < .05$, nephrectomized placebo-treated and immunosuppressed rats day 2 *v* placebo-treated controls day 0. **$P < .05$, immunosuppressed nephrectomized and control rats *v* placebo-treated nephrectomized and immunosuppressed nephrectomized rats, respectively, at the end of the study period. (C) Changes in serum IGFBP-4. *$P < .05$, nephrectomized placebo-treated and immunosuppressed rats day 2 *v* placebo-treated controls day 0.

Table 1. Supplemental Study (study 2) of the Effect of 7-Day Treatment With Placebo, CsA, or Prednisolone in Sham-Operated Controls and Nephrectomized Rats at the End of the Study Period

Parameter	Sham-Operated Controls			Nephrectomized Rats		
	Placebo	CsA	Prednisolone	Placebo	CsA	Prednisolone
BW (g)	211 ± 2*	194 ± 4	180 ± 2†	208 ± 3*	187 ± 2	172 ± 4†
Kidney weight (mg)	741 ± 27‡	694 ± 11‡	712 ± 26‡	885 ± 11	795 ± 17§	867 ± 28
Kidney weight/100 g BW	351 ± 11	358 ± 6	397 ± 17	429 ± 9	425 ± 11	503 ± 11
Food intake (g/24 h)	18 ± 1‖	15 ± 1	13 ± 1	18 ± 1‖	12 ± 1	15 ± 1
Kidney IGF-I (ng/g)	451 ± 29	335 ± 19¶	438 ± 28	651 ± 65#	395 ± 25	616 ± 40#
Serum IGFBP-3 AU/mm²	245 ± 9	265 ± 18	278 ± 20	264 ± 24	281 ± 20	324 ± 22
Serum 30-kd IGFBPs AU/mm²	29 ± 4**	36 ± 5	53 ± 10	34 ± 6	35 ± 5	69 ± 9
Serum IGFBP-4 AU/mm²	12 ± 1††	17 ± 4	17 ± 4	29 ± 5	23 ± 3	27 ± 4
Serum IGF-I (μg/L)	775 ± 46	684 ± 33	792 ± 11	890 ± 44‡‡	823 ± 20	882 ± 47‡‡

*$P < .05$, placebo-treated control and nephrectomized rats *v* all other groups.

†$P < .05$, prednisolone-treated controls and nephrectomized rats *v* placebo-treated rats or CsA-treated control and nephrectomized rats, respectively.

‡$P < .05$, the 3 control groups *v* nephrectomized rats.

§$P < .05$, CsA-treated nephrectomized rats *v* placebo- and prednisolone-treated nephrectomized rats.

‖$P < .05$, placebo-treated control and nephrectomized rats *v* all other groups.

¶$P < .05$, CsA-treated controls *v* placebo-treated controls.

#$P < .05$, nephrectomized placebo- and prednisolone-treated rats *v* all other groups.

**$P < .05$, placebo-treated control rats *v* prednisolone-treated control and nephrectomized rats.

††$P < .05$, placebo-treated control rats *v* nephrectomized placebo- and prednisolone-treated rats.

‡‡$P < .05$, nephrectomized placebo- and prednisolone-treated rats *v* placebo-treated controls.

to diminished bioactivity. In addition, circulating IGFBP-1 and IGFBP-2 have been demonstrated to have inhibitory actions themselves on IGFs (for review, see Bach and Rechler[32]). However, the growth retardation observed in CsA-treated animals by the present data seems not to be caused via an influence on circulating IGF-I or IGFBP levels.

Serum IGFBP-4 derived primarily from the liver and is GH-independent, as demonstrated by hypophysectomy[33] and in GH-deficient dwarf rats.[34] In the present study, uninephrectomy was followed by a transient (study 1) or sustained (study 2) increase in the serum IGFBP-4 band, with no changes observed in controls and no effect of immunosuppression per se. It therefore seems to be an effect mediated by the reduction in renal mass, and suggests that IGFBP-4 is excreted to some extent via the kidney. This has been demonstrated more directly in a recent experiment wherein a positive correlation between the serum IGFBP-4 level and the amount of renal tissue resected was demonstrated.[18] The effect of IGFBP-4 seems exclusively inhibitory on IGF-I actions as demonstrated in vivo[35] and in vitro.[36,37] However, in the present experiment, there was no relationship between the increase in IGFBP-4 and BW.

In conclusion, uninephrectomy followed by immunosuppression with prednisolone and CsA, approaching the clinical situation in the early phase after kidney transplantation, induced a small but significant reduction in kidney IGF-I accumulation and compensatory renal hypertrophy after the unilateral nephrectomy. The reduction in renal IGF-I accumulation and renal growth seems to be mediated by CsA, while prednisolone treatment alone did not affect renal growth or IGF-I levels. In addition, immunosuppression was followed by an inhibition of BW gain along with an increase in circulating levels of IGFBP-3 and 30-kd IGFBPs (IGFBP-1 and IGFBP-2), however, without significant changes in total serum IGF-I. The effect on circulating IGFBPs was predominantly caused by prednisolone treatment, whereas CsA had no effect on serum IGFBPs. The increase in IGFBPs may induce a reduction in IGF bioactivity and thus be partly involved in the observed reduced BW increase.

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