Pediatr Nephrol (1998) 12: 408–413

Pediatric Nephrology

Original article

Renal tubular dysgenesis in twins

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Received February 7, 1997; received in revised form and accepted December 15, 1997

Abstract. In a fetal autopsy series, we have explored the occurrence of renal tubular dysgenesis in twins. Renal tubular dysgenesis was found exclusively among those monozygotic twins with evidence of twin transfusion syndrome, particularly in those donor twins with oligohydramnios and growth restriction. We infer that hypotension in the donor twin of the twin transfusion syndrome pair is responsible for the failure of proximal convoluted tubule differentiation, and the disturbance of renal function is manifested as oligohydramnios prenatally, and either oliguria or tubular dysfunction postnatally.

Key words: Twins – Renal tubular dysgenesis – Prenatal injury

Introduction

Renal tubular dysgenesis (RTD) is characterized by diminished to absent differentiation of proximal convoluted tubules (PCTs) [1], which are shorter and straighter than normal [2]. There may also be increased cortical and medullary mesenchyme (and later fibrosis) and dilation of Bowman's spaces and tubules. The histological changes in the kidney strongly suggest ischemic injury, with the added component of deficient tubular differentiation.

In addition to its occurrence as a hereditary syndrome, RTD is a characteristic finding in angiotensin-converting enzyme (ACE) inhibitor fetopathy [3]. We hypothesized that the failure of PCT differentiation in RTD is a result of renal hypoperfusion, due to fetal hypotension, or altered hemodynamics within the kidney [4, 5]. To look for supporting evidence, we examined the kidneys of midgestation twins, a number of whom were affected by the twin transfusion syndrome.

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Materials and methods

The study comprised autopsy data from 128 twins with no major malformations and minimal to no maceration. Included were 26 dizygous fetuses (DZ, 13 pairs, different sex), 56 fetuses of unknown zygosity (UZ, 28 pairs, like sex and no significant discrepancy in size but no placental information), and 46 monozygous fetuses (MZ, 21 pairs and 4 individual donor twins). Postmenstrual ages ranged from 16.1 to 28.6 weeks.

Z-scores (observed – expected/standard deviation) of body, brain, heart, and kidney weights were calculated from normative data collected at the Universities of Michigan and South Alabama [6]. Because the variance of measurements about the mean expands with fetal growth, the Z-score method permits standardization across different fetal ages [6]. A sample of normal, or typical for age, singleton fetuses in the same age range as the twin sample was used as controls for comparing visceral weights. Larger and smaller twins were compared with the controls separately using two-tailed *t*-tests (Table 1). Larger and smaller twins were compared with each other using paired *t*-tests (Table 2).

Microscopic sections of kidneys were examined, without knowledge of the clinical characteristics of the fetus, for the presence or absence of PCT differentiation (Fig. 1).

Additionally, number of glomeruli in a ×400 microscopic field was determined, just inward from the zone of nephrogenesis, using the mean of 15 fields from each fetus. This count is a reflection of the increased density of glomeruli that results from the absence of space-occupying, normally developed PCTs.

Results

Among the DZ and UZ twins, no significant deviation from the expected mean was found for heart or kidney weights, and there were no significant differences between the larger and smaller twins (Fig. 2). Brain weights of the DZ and UZ twins were comparable to controls, but there were small but statistically significant differences when larger twins were compared with smaller twins by paired *t*-test (Table 2). Among the MZ twins, there was significant sparing of brain growth in the smaller twin and a much heavier heart in the larger twin [7] (Fig. 2). In the smaller twins, the heart and kidneys were markedly light for brain weight standards, but less so for body weight standards.

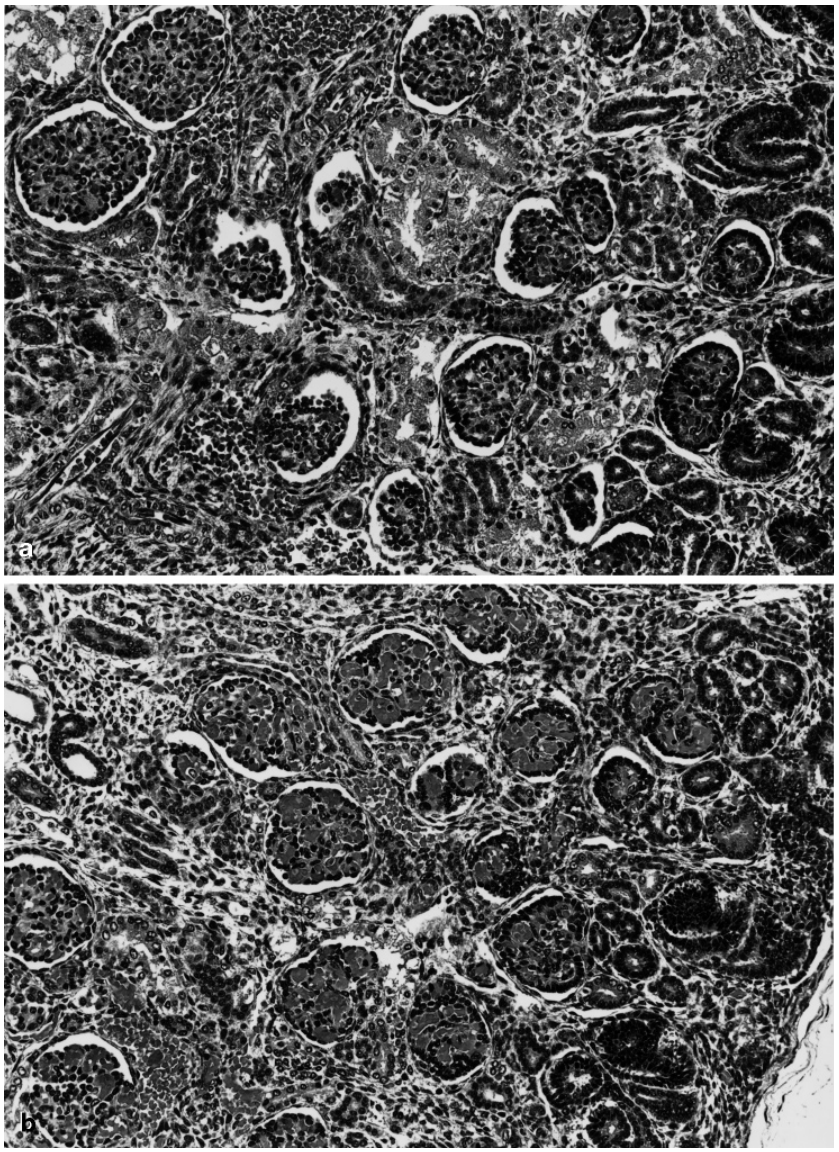

Fig. 1 a, b. Renal cortex in twin transfusion syndrome at 22.1 postmenstrual weeks.
a Recipient twin: glomeruli intermingled with normal proximal convoluted tubules (PCTs).
b Donor twin: glomeruli appear more numerous due to the absence of differentiated PCTs between them. In both **a** and **b** immature glomeruli are to the right, progressing to mature glomeruli on the left (hematoxylin and eosin, ×155)

Heart and brain weight discrepancies were used as a marker for twin transfusion syndrome: a large heart in the recipient twin and a heavy brain for body weight in the donor twin. There were 17 sets of MZ twins that had such evidence of twin transfusion syndrome, to which we added the 4 individual donor twins. There were 4 sets of MZ twins that were unaffected by the twin transfusion syndrome and had visceral weight profiles similar to the DZ twins. Comparing donor twins with (10) and without (11) PCT differentiation, those without PCT differentiation showed somewhat more growth restriction of brain, heart, and kidney (Fig. 2), and their mean glomerular counts were higher (9.2 vs. 7.1) (Fig. 3). Among the DZ and UZ twins, all had differentiated PCTs, and their mean glomerular counts (6.6–6.9) were very similar (Fig. 3).

Among the MZ twins, oligohydramnios was cited in the clinical information of 6 donor twins. Their mean glomerular count was 8.3; 3 had no PCT differentiation and their mean glomerular count was 9.6. In an additional 9 MZ twin sets, polyhydramnios was reported without distinguishing whether one or both twins were affected. From the presence of compressional deformation of the face, hands, and feet, oligohydramnios was inferred for 6 individual twins (all donors) among these 9 sets. None of these 6 twins had PCT differentiation and their mean glomerular count was 9.6. The other 3 had PCT differentiation and their mean glomerular count was 7.1.

Discussion

RTD is a characteristic feature of ACE inhibitor fetopathy. RTD has been fully described in four cases of ACE inhibitor fetopathy [3, 8]. It was probably the lesion in the case reported by Knott et al. [9], and it has been observed in a number of unreported cases. The renin angiotensin system becomes crucially important under conditions of low renal perfusion pressure [10, 11]. Under these conditions, which pertain to the fetus, angiotensin II-mediated efferent arteriolar resistance is essential to the maintenance of glomer-

Table 1. Comparison by two-tailed *t*-test of Z-scores of control fetuses with larger and smaller twins

		Larger twin			Smaller twin		
		t	df	*P*	*t*	df	*P*
Control vs. DZ	BRNBDY	1.641		0.10	–1.080		0.28
	HRTBDY	1.104		0.27	0.696		0.49
	KIDBDY	–0.674	634	0.50	–0.134	634	0.89
	HRTBRN	0.104		0.92	1.326		0.19
	KIDBRN	–1.458		0.15	0.208		0.84
Control vs. UZ	BRNBDY	–0.090		0.93	–2.731		0.0065
	HRTBDY	–1.468		0.14	–1.609		0.11
	KIDBDY	0.570	649	0.57	–0.702	649	0.48
	HRTBRN	–1.484		0.14	0.028		0.98
	KIDBRN	0.387		0.70	0.583		0.56
Control vs. MZ	BRNBDY	–0.473		0.64	–9.827		0.0000000
	HRTBDY	–14.773		0.0000000	3.091		0.0021
	KIDBDY	–3.109	643	0.0020	3.336	646	0.00090
	HRTBRN	–15.203		0.0000000	7.314		0.0000000
	KIDBRN	–2.999		0.0028	4.584		0.0000055
Control vs. MZ with TTS	BRNBDY	–1.230		0.22	–10.127		0.0000000
	HRTBDY	–17.622		0.0000000	2.241		0.025
	KIDBDY	–3.854	639	0.00013	2.498	641	0.013
	HRTBRN	–17.569		0.0000000	6.917		0.0000000
	KIDBRN	–3.321		0.00095	4.141		0.000039
Control vs. MZ, smaller with no PCT	BRNBDY	–0.467		0.64	–9.044		0.0000000
	HRTBDY	–14.487		0.0000000	3.692		0.0024
	KIDBDY	–2.046	631	0.041	3.368	632	0.00080
	HRTBRN	–14.332		0.0000000	6.851		0.0000000
	KIDBRN	–1.875		0.061	4.251		0.000025

DZ, Dizygous; UZ, unknown zygosity; MZ, monozygous; TTS, twin transfusion syndrome; PCT, proximal convoluted tubule differentiation; BRNBDY, brain weight for body weight standards; HRTBDY and HRTBRN, heart weight for body and brain weight standards respectively; KIDBDY and KIDBRN, kidney weight for body and brain weight standards respectively

ular filtration and production of urine [12, 13]. ACE inhibitors reduce glomerular filtration pressure by dilating the glomerular efferent arterioles. How this might affect differentiation of PCTs is not certain. While type 1 angiotensin II receptors mediate all the known effects of angiotensin related to the renin angiotensin system, type 2 receptors appear to be involved in the development of the kidney [14, 15]. Suppression of their function by ACE inhibition may affect tubular differentiation.

RTD has also been reported as a congenital autosomal recessive disease, with oligohydramniotic deformation and pulmonary hypoplasia [1, 2, 16, 17]. Bernstein and Barajas [18] demonstrated increased renin in preglomerular arterioles, glomerular hila, and mesangial areas in the hereditary form of RTD. The renin accumulation suggested faulty feedback control of renin secretion in this variety of RTD. They hypothesized that the increased renin accumulation reflected strong local vasoconstriction resulting in reduced glomerular perfusion, which would link it to the RTD seen in ACE inhibitor fetopathy.

Possible support for the renal ischemia hypothesis comes from Landing et al. [19] who noted that RTD has been seen as a unilateral lesion in young infants with renal artery stenosis due to arteritis or medial arterial calcinosis, and that it resembles the renal tubular atrophy of a variety of end-stage kidney diseases, such as glomerulonephritis, tubulointerstitial kidney disease, obstructive uropathy, and pyelonephritis, graft rejection of transplanted kidneys, and the renal parenchymal changes associated with protracted dialysis therapy. Landing et al. [19] reported that labelled lectins that differentially mark proximal convoluted, distal convoluted, connecting, and collecting tubules showed no distinctive differences in the staining patterns of the hypoplastic renal tubules in RTD compared with kidneys affected by postnatal renal artery obstruction or various types of end-stage renal disease. These findings suggest that the renal tubular changes in the conditions cited result from renal ischemia.

However, the issue of mechanism is far from settled and may be more complicated than renal ischemia leading directly to RTD. In the fetal sheep, when renal oxygen delivery was limited by a prolonged reduction in hematocrit, sodium and water excretion increased and resulted in an *increase* in amniotic fluid volume [20], in contrast to the oligohydramnios seen in ACE inhibitor fetopathy. Thus, it would appear that, in the case of ACE inhibitor exposure, the initiating event for RTD may be a derangement of both fetal physiology and function of the renin-angiotensin system by the drug, which may secondarily interfere with differentiation of PCTs.

When examining the specificity of this set of histopathological findings for ACE inhibitor exposure, Martin et al. [4] studied the fetuses of women who were chronically hypertensive. Three of these mothers used antihypertensive agents throughout pregnancy, including 1 who used an ACE inhibitor. The tubular morphology of the kidneys was

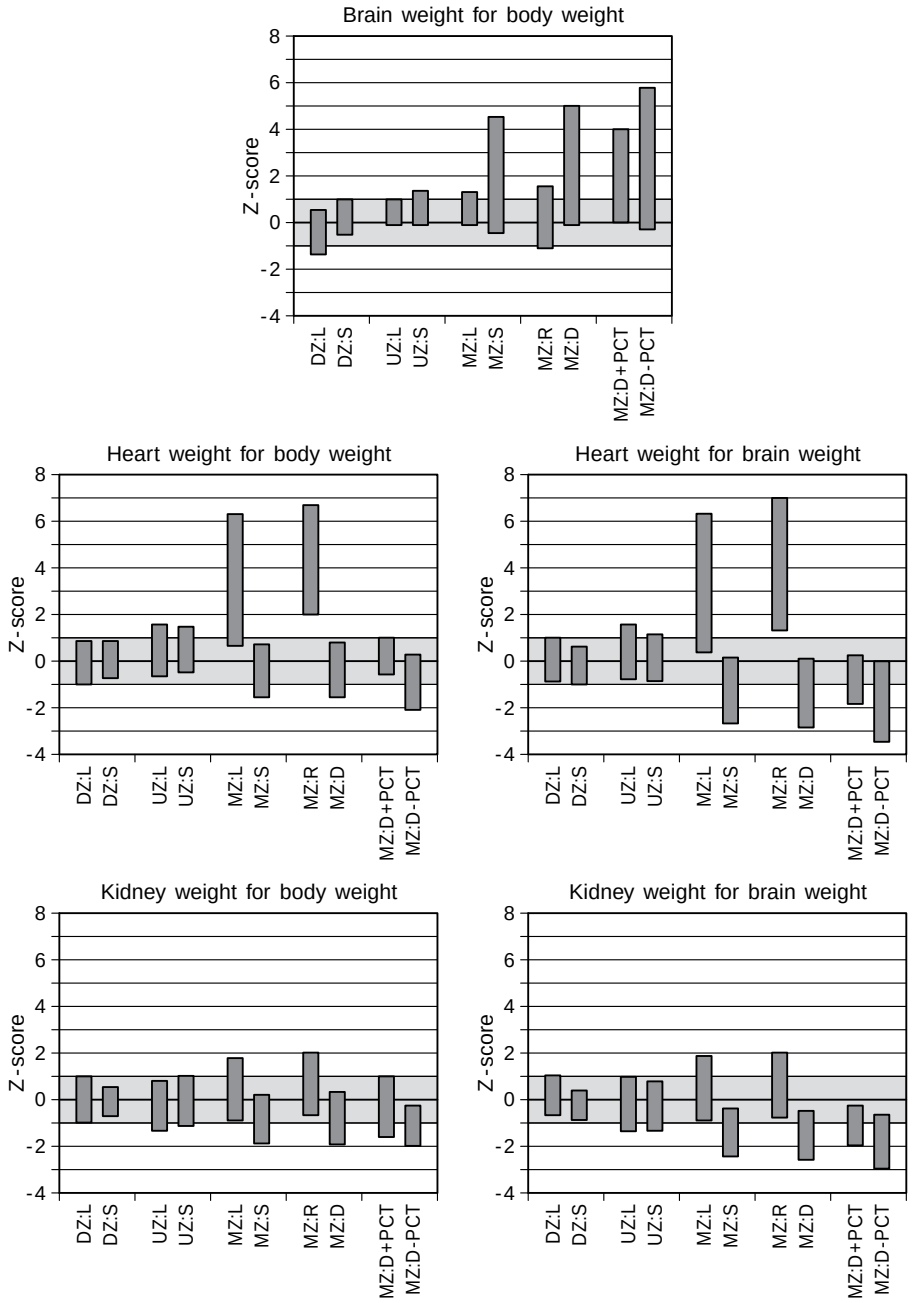

Fig. 2. Z-scores of brain, body, heart, and kidney weight by twin type or characteristic. The *bars* represent the observed mean ± 1 SD, with the normal range (mean ± 1 SD) indicated by the *shaded area*. *DZ*, Dizygous; *UZ*, unknown zygosity; *MZ*, monozygous; *L*, larger twin; *S*, smaller twin; *R*, recipient twin; *D*, donor twin

compared with the renal tubules of 20 normal controls, 13 fetuses with various multiple malformation syndromes, and 6 cases of the twin transfusion syndrome. Features of RTD were identified in the ACE inhibitor-exposed case, 1 methyldopa-exposed case, and 2 cases of twin transfusion syndrome [4].

Twinning occurs in approximately 1 in 90 births. Of these about 30% are monozygous, the vast majority of which are monochorionic [21]. Among monochorionic twins, 85%–100% have intraplacental vascular anastomoses, approximately 30% of whom will have evidence of circulatory imbalance known as the twin transfusion syndrome [22].

Hawkins et al. [23] noted that three of five donor twins they examined had a decreased percentage of PCTs. Genest and Lage [24] reported 6 examples of absent PCTs among 500 perinatal autopsies; 3 were twins with the twin transfusion syndrome. We surmised that the circulatory imbalance found in the twin transfusion syndrome is likely to reduce renal perfusion and glomerular perfusion pressure in the donor twin. If this were true, and by analogy with the mechanism in ACE inhibitor fetopathy, RTD could be expected to result. We found failure of PCT differentiation in 11 of 21 donor twins but in none of 17 recipient twins, 26 DZ twins, or 56 twins of unknown zygosity without evidence of twin transfusion syndrome.

RTD is found in ACE inhibitor fetopathy, hereditary RTD, and donor twins of the twin transfusion syndrome. These three lines of evidence suggest that alteration of glomerular perfusion can result in impaired differentiation of PCTs, manifested as RTD.

Table 2. Comparison by paired *t*-test of Z-scores of twins within sets

	BRNBDY					
	t	df			*P*	
DZ L vs. S	–3.274	12			0.0067	
UZ L vs. S	–3.661	27			0.0011	
MZ L vs. S	–4.269	21			0.00034	
TTS R vs. D	–4.064	17			0.00081	
+PT vs. –PT	–3.499	9			0.0067	
	HRTBDY			HRTBRN		
	t	df	*P*	*t*	df	*P*
DZ L vs. S	–0.555	12	0.59	1.672	12	0.12
UZ L vs. S	–0.164	27	0.87	1.735	27	0.094
MZ L vs. S	6.668	21	0.0000013	7.179	21	0.0000004
TTS R vs. D	8.421	17	0.0000002	8.744	17	0.0000001
+PT vs. –PT	7.186	9	0.000052	7.959	9	0.000023
	KIDBDY			KIDBRN		
	t	df	*P*	*t*	df	*P*
DZ L vs. S	0.614	12	0.55	1.758	12	0.10
UZ L vs. S	–1.138	27	0.27	0.172	27	0.86
MZ L vs. S	4.256	21	0.00035	4.421	21	0.00024
TTS R vs D	4.224	17	0.00057	4.340	17	0.00044
+PT vs –PT	3.743	9	0.0046	3.849	9	0.0039
	MGC					
	t	df			*P*	
DZ L vs. S	0.273	12			0.79	
UZ L vs. S	–0.320	27			0.75	
MZ L vs. S	–3.651	21			0.0016	
TTS R vs. D	–3.815	17			0.0015	
+PT vs. –PT	–5.512	9			0.00057	

L, Larger; S, smaller; R, recipient; D, donor; MGC, mean glomerular count

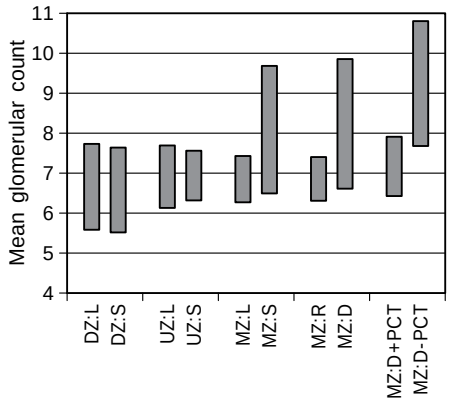

Fig. 3. Mean glomerular counts by twin type or characteristic. The *bars* represent the mean ± 1 SD. Higher counts are a reflection of increased density of glomeruli resulting from the decreased bulk of differentiated PCT

This study indicates that the prenatal marker for the MZ twin likely to have RTD is the combination of growth restriction and oligohydramnios. In such circumstances, pulmonary hypoplasia is a common finding. However, these findings have implications for more than the prenatal and immediate neonatal prognosis of twins, for significant postnatal renal morbidity may occur in the affected donor twin. Infants with twin transfusion syndrome can have a classic picture of acute tubular necrosis with full recovery, marked decrease in renal perfusion leading to cortical necrosis and renal failure, or permanent tubular dysfunction with polyuria, most compatible with tubular dysgenesis.

For many, the problems these infants experience are not due just to acute tubular necrosis acquired in the neonatal period, but are a consequence of a developmental defect originating in midgestation. The challenge will be to see if a means to prevent the occurrence of RTD in MZ twins can be devised.

Acknowledgement. We express our appreciation to the many parents who so generously gave permission to examine their babies in the hope that some good might come of their misfortune.

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Literature abstract

Kidney Int (1997) 52: 802–810

Insulin-like growth factors (IGFs) and IGF binding proteins, serum acid-labile subunit and growth hormone binding protein in nephrotic children

Dieter Haffner, Burkhard Tönshoff, Werner F. Blum, Marc Vickers, Thomas Siebler, Michael J. Cronin, Robert C. Baxter, and Otto Mehls

We hypothesized that the increased glomerular permeability to serum proteins in the nephrotic syndrome might lead to alterations of the somatotropic hormone axis, thereby contributing to growth failure and catabolism in the nephrotic state. The insulin-like growth factors (IGF)-I and -II and the IGF binding proteins (IGFBP)-1, -2 and -3 were analyzed in serum and urine of 21 children with the nephrotic syndrome and normal glomerular filtration rate. Mean age-related serum IGF-I levels by RIA (–0.53 ± 0.34 SD) were slightly, but significantly ($P < 0.05$) decreased compared with the reference population, whereas mean age-related serum IGF-II levels (0.68 ± 0.21 SD) were slightly, but significantly ($P < 0.005$) increased. The urinary excretion rate of both peptides was enhanced fivefold. By RIA, mean age-related serum IGFBP-1 (2.05 ± 0.19 SD) and, even more pronounced, IGFBP-2 (5.97 ± 0.65 SD) were clearly elevated despite a 12-fold and 2-fold increase of the respective urinary excretion rate. There was a tight and specific correlation between age-related serum IGFBP-2 levels and the degree of the nephrotic syndrome, as estimated by serum albumin levels ($r = 0.78$, $P < 0.0001$). Serum immunoreactive IGFBP-3 levels were also elevated (1.79 ± 0.33 SD) in nephrotic serum, due to an increase of low-molecular weight IGFBP-3 fragments. By FPLC analysis, there was a decrease of the 150 kDa IGFBP ternary complex in nephrotic serum, which in the presence of normal concentrations of the acid-labile subunit by RIA appears to be due to a reduction of intact IGFBP-3. Serum levels of the high-affinity GH binding protein that presumably reflects GH receptor status in tissues were normal. In summary, total serum IGFs in children with the nephrotic syndrome are normal, but the binding of IGFs to IGFBPs in the circulation is altered with a shift from the 150 kDa IGFBP complex to an excess of low molecular weight IGFBPs. Because increased unsaturated high-affinity IGFBPs in nephrotic serum have the ability to inhibit IGF action on target tissues by competing with the type 1 IGF receptor for IGF binding, this alteration is likely to contribute to growth failure and tissue catabolism in the nephrotic state.