

Title: Congenital reduction in number of nephrons accelerates renal damage, and limits proximal tubular growth response to release of neonatal partial ureteral obstruction

Aim: to analyze the evolution of the response to persistent partial ureteral obstruction (PUO) and obstruction/release (PUO/Rel) in mice with 50% reduction in the number of nephrons from 21 days of age (time of weaning) to 42 days of age (adulthood).

Methods: C57/BL6 wild-type (WT) and mice with oligosyndactylism and 50% reduction of nephron number (Os/+), were subjected to sham operation or PUO in the first 2 days of life. Additional mice underwent release of obstruction at 7 days (PUO-Rel). The study was performed in kidneys harvested at 21 and 42 days. Using histomorphometry, glomerular area (GA) was determined by PAS staining, and fractional proximal tubular (PT) mass and intact glomerulotubular junctions (GTJ) were measured in *Lotus tetragonolobus* lectin-stained kidneys.

Results:

	WT Sham 21 vs 42 d	Os Sham 21 vs 42 days	WT PUO 21 vs 42 d	Os PUO 21 vs 42 d	WT PUO/Rel 21 vs 42 d	Os PUO/Rel 21 vs 42 d
Kidney weight, g	58 vs 135 *	30† vs 80† *	42 vs 107 *	22 vs 55† *	59 vs 101 *	33 vs 59† *
Glomerular area, 10 ⁻³ μm ²	2.2 vs 3.4 *	2.7 vs 5.0† *	1.8 vs 2.9 *	2.1‡ vs 3.3‡ *	2.3 vs 2.6‡	2.1‡ vs 3.0‡ *
PT %	43 vs 61 *	48† vs 68† *	34 vs 40‡	46 vs 43‡	45 vs 60 *	45 vs 54‡
Intact GTJ %	52 vs 70 *	48 vs 62† *	30‡ vs 41‡	36‡ vs 45‡	50 vs 62	50 vs 53

Mean per group (n = 6-14 mice per group). P<0.05 †vs WT, ‡vs sham, *vs 21 d

Body weight doubled and kidney weight increased ~50% from 21 to 42 days of age in all mice. At 42 days, kidney weight was lower in Os/+ than WT kidneys, regardless of obstruction. Glomerular area increased with age in all groups except in WT PUO/Rel. In contrast to WT, glomerular area was reduced by PUO in Os/+ mice at both 21 and 42 days. Fractional PT mass increased with age of sham-operated mice, but this was prevented by PUO in both strains. Release of obstruction prevented the decrease of PT mass in 42 day-old WT, but not in Os/+ mice. Fraction of intact GTJ increased with age in sham kidneys in both strains, but did not increase in obstructed kidneys regardless of release. Intact GTJ % was decreased by PUO in both strains regardless of age; this was prevented by release of obstruction.

Conclusions: PUO impaired glomerular growth in Os/+ but not WT mice, and prevented GTJ maturation and PT growth in both strains. Release of obstruction had no effect on glomerular area, allowed GTJ maturation in both strains, and permitted PT growth in WT but not Os/+ mice. Because preterm and intrauterine growth-restricted infants are born with reduced nephron number, these patients may be at greater risk for renal injury due to urinary tract obstruction.