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Birth Weight as a Marker of Nephron Number: Predicting Living Kidney Donor Outcomes

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INTRODUCTION

Very recent studies suggest that living kidney donors face an increased risk of end-stage renal disease, cardiovascular disease, and overall mortality as a result of the reduction of nephron number by unilateral nephrectomy. Since a method to assess the number of functioning nephrons has not been developed to identify individuals with a reduced nephron number, low birth weight as the best surrogate marker of nephron number needs to be evaluated in the context of living kidney donation. Here, the substantial variability in nephron number across the otherwise healthy population of donors suggests an impact of renal mass on living kidney donor outcomes. Previous studies on renal development showed that nephrogenesis markedly increases in the third trimester and reaches completion at approximately 34 to 36 weeks of gestation, after which only loss of nephrons by aging, disease, or trauma occurs. Infants born during active nephrogenesis before completion at 34 to 36 weeks of gestation will have a reduced nephron number proportional to their birth weight. In addtion a strong relationship between low birth weight and the development of essential hypertension and cardiovascular disease has been proposed.

PATIENTS AND METHODS

We followed up 91 living kidney donors for at least 12 months. To assess the effect of nephron number on the outcomes of donors after living kidney donation we looked at donor birth weight, donor serum uric acid levels, donor kidney weight, donor kidney volume, body surface area, bodyweight, and body-mass-index. Here, we tried to address the following open questions: (1) What is the impact of donor birth weight on the outcome of donor renal function? (2) What is the impact of donor birth weight on the development of hypertension in the donor? (3) What is the impact of donor birth weight on the development of proteinuria in the donor?

	All donors (n=91)	Donor birth weight ≤2.5kg (n=18)	Donor birth weight >2.5kg (n=73)	*P value*
Age, yr *	53 (20-78)	53 (20-71)	52 (27-78)	*0.326*
Male, n (%)	31 (34)	8 (44)	23 (32)	*0.405*
Body weight, kg *	70 (45-113)	72 (65-89)	70 (45-113)	*0.182*
Body surface area, m^2	1.79 (1.42-2.33)	1.83 (1.66-2.13)	1.78 (1.42-2.33)	*0.151*
BMI, kg/m^2	25 (18-38)	27 (23-31)	25 (18-38)	*0.124*
≤ 25, n (%)	37 (41)	5 (28)	32 (44)	*0.287*
26-30, n (%)	48 (53)	11 (61)	37 (51)	*0.599*
> 30, n (%)	6 (7)	2 (11)	4 (5)	*0.339*
Smoking, n (%)	10 (11)	0 (0)	10 (14)	*0.201*
Hypertension, n (%)	35 (38)	12 (66)	23 (32)	***0.013****
Onset pretransplant	17 (19)	5 (28)	12 (16)	*0.314*
Onset posttransplant	18 (20)	7 (39)	11 (15)	***0.043****
Proteinuria pretransplant, mg/d*	49 (10-98)	49 (10-98)	49 (40-72)	*0.788*
Proteinuria at +12 months, mg/d*	130 (42-256)	169 (107-256)	128 (42-233)	***0.004****
Uric acid pretransplant, mg/dL*	4.9 (2.1-8.3)	5.1 (3.8-8.3)	4.7 (2.1-7.9)	***0.003****
Uric acid posttransplant, mg/dL*	5.8 (3.5-10.2)	6.0 (4.9-8.9)	5.6 (3.5-10.2)	***<0.001****
Cardiovascular events pretransplant	0 (0)	0 (0)	0 (0)	-
Myocardial infarction n (%)	0 (0)	0 (0)	0 (0)	
Stroke, n (%)	0 (0)	0 (0)	0 (0)	
Cardiovascular events posttransplant	2 (2)	1 (6)	1 (1)	*0.358*
Myocardial infarction, n (%)	1 (1)	1 (6)	0 (0)	
Stroke, n (%)	1 (1)	0 (0)	1 (1)	
Remaining kidney volume, cm^3	158 (102-227)	163 (117-227)	153 (102-220)	*0.639*
Remaining kidney weight, g	175 (108-293)	177 (128-288)	175 (108-293)	*0.536*
Remaining kidney weight/dBSA, g/m^2	99 (68-161)	103 (77-143)	99 (68-161)	*0.415*
Remaining kidney scintigraphy, %	53.3 (41.4-63.1)	55.0 (44.4-63.1)	52.1 (41.4-63.1)	*0.754*
Donor birth weight, g	3200 (1500-5600)	2000 (1500-2500)	3400 (2600-5600)	-

RESULTS

Figure 1A Strong positive correlation between estimated GFR and donor birth weight at +12 months after nephrectomy. **1B** Strong positive correlation between estimated GFR and donor birth weight at +12 months in donors above the age of 50 years. **2C** Modest positive correlation between estimated GFR and donor birth weight at +12 months in donors below the age of 50 years.

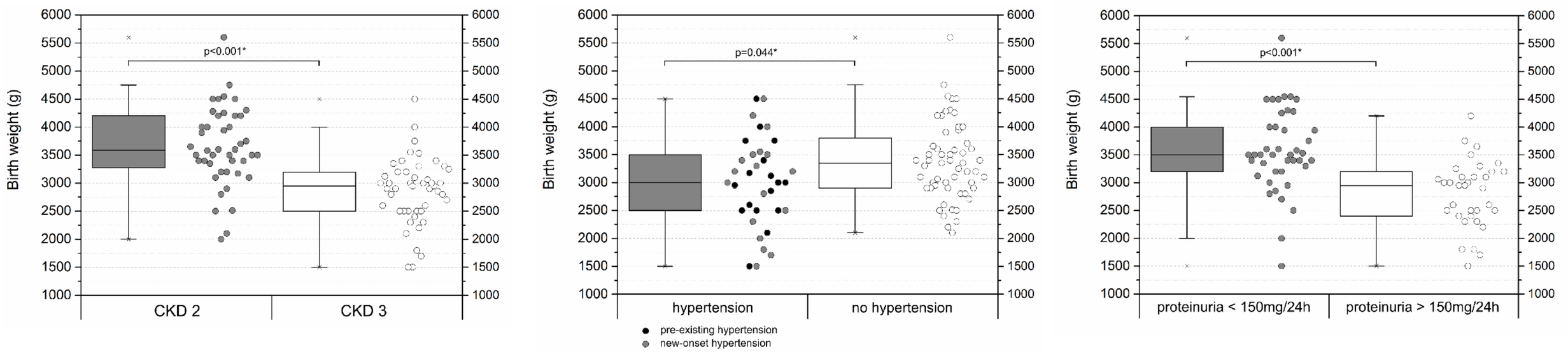

Figure 2A-C. 2A Significantly higher birth weight in donors that meet criteria of chronic kidney disease stage 2 compared to stage 3 at +12 months after nephrectomy. **2B** Significantly higher birth weight in donors with pre-existing or new-onset hypertension after donor nephrectomy. **2C** Significantly higher birth weight in donors with proteinuria < 150mg/24h at +12 months after nephrectomy.

CONCLUSIONS

1. **Strong relationship between donor birth weight as a marker of nephron number and remaining kidney function.** Our data suggest a strong relationship between donor birth weight as a marker of nephron number and the remaining kidney function. Our data show the strongest relationship between donor birth weight and remaining kidney function in elderly donors. This observation may be attributed to the continuous loss of glomeruli with age with a mean predicted loss of approximately 4500 glomeruli per kidney per year starting in the third decade of life. The natural decline of renal function with age with reduced renal functional reserve in elderly donors may contribute to the strong correlation in elderly donors.
2. **Strong relationship between donor birth weight as a marker of nephron number and the development of proteinuria.** Our data suggest that low birth weight as a marker of nephron endowment has significant effects on the amount of daily proteinuria and the development of hypertension after donation. Previous works showed higher rates of microalbuminuria in patients of low birth weight independet of the presence or absence of diabetes mellitus.
3. **Strong relationship between donor birth weight as a marker of nephron number and the development of hypertension.** Our data suggest that low birth weight as a marker of nephron endowment has significant effects on the development of hypertension after donation. it has been proposed that people with lower glomerular numbers are more susceptible to hypertension, which is initiated and propagated through the cascade of events that follows compensatory nephron hypertrophy. In this context our data on increased serum uric acis levels in donors developing hypertension support previous observations, that an elevation in serum uric acid levels has a major role in the pathogenesis of hypertension.

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