Pediatr Nephrol (2009) 24:1363–1370
DOI 10.1007/s00467-009-1120-2

ORIGINAL ARTICLE

Obesity and preterm birth: additive risks in the progression of kidney disease in children

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Received: 31 August 2008 / Revised: 23 November 2008 / Accepted: 15 December 2008 / Published online: 12 February 2009

Abstract Preterm birth is associated with decreased nephron mass and obesity that may impact on kidney disease progression in later life. Our objectives were to examine the relative risks of obesity and preterm birth on the progression of kidney disease in children. In a retrospective cohort study, 80 (44 obese and 36 non-obese) patients with proteinuric kidney disease were studied for disease progression and glomerular histomorphometry. Of the obese, 22 had been born at term (Obese-T) and 22 had been preterm (Obese-PT). Seventeen non-obese children with focal glomerular sclerosis, born at term (NO-FSGS), and 19 non-obese preterm (NO-PT) children, served as controls. Insulin resistance as measured by the homeostatic model assessment (HOMA-IR) was elevated in all obese children. Obese-PT patients had increased risk of renal demise during childhood when compared with Obese-T children [hazard ratio 2.4; 95% Confidence interval (95% CI) 1.1 to 7.1; $P=0.04$]. In obese children, although proteinuria often exceeded nephrotic range, average levels of serum albumin remained normal. Preterm patients were more likely to have reduced renal mass (odds ratio 4.7; $P=0.006$), but obesity was not a factor. Renal histomorphometry showed glomerulomegaly in obese patients, regardless of birth weight. Obesity and preterm birth appear to impose additive risks for progression of kidney disease in childhood.

Keywords Low birth weight · Obesity · Chronic kidney disease · Prematurity · Glomerulomegaly · Histomorphometry

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Introduction

Concomitant with the global obesity epidemic [1], there are a number of reports of obesity-related glomerulopathy (ORG) associated with progression of kidney diseases in adults and adolescents [2–5]. Some of these reports note a decrease in nephron mass by acquired unilateral nephrectomy or established renal disease [2, 4, 6–10]. ORG in adults has been defined as the clinical syndrome of morbid obesity, marked proteinuria without edema and normal serum albumin [3]. Histomorphometry describes glomerulomegaly which is thought to reflect glomerular hyperfiltration [8–10].

In the context of pediatric kidney disease, reduced nephron mass and increased risk for end-stage kidney disease (ESKD) has been associated with individuals born small for gestational age (SGA) as well as those born preterm and appropriate for gestational age (AGA) [11–13]. Epidemiologic studies indicate that low birth weight in conjunction with rapid post-natal growth imposes an increased risk for hypertension, insulin resistance and type 2 diabetes in later life [13, 14]. Some ethnic populations, such as the Aborigines [15], American Indians [16], and African Americans of the southeast United States of America [17], develop proteinuric kidney disease associated with hypertension and glomerulomegaly, presumably related to reduced nephron mass [18]. Our previous clinical observations suggest that early excessive weight gain

contributes to progression of kidney disease in patients who have suffered neonatal acute kidney injury (AKI) [19]. It remains unclear whether these manifestations are the results of "developmental programming" induced by adverse environmental events in utero or during the vulnerable periods in early post-natal life [20]. The population of surviving low birth weight individuals born preterm are the focus of much research, since they offer some insight into this phenomenon as regards glucose sensitivity [21, 22], low nephron mass [12, 13] and cardiovascular disease risk [23, 24]. This problem has become increasingly more evident in the multi-ethnic community of South Florida, with a growing population of children with obesity-related non-diabetic kidney disease. We have had an opportunity to examine a cohort of pediatric patients with chronic kidney disease (CKD) born preterm and have compared them with those born of normal birth weight with and without obesity according to renal disease progression and histomorphometry. To our knowledge, this report is the first to describe clinico-pathologic correlations of this kind in children.

Patients and methods

Patient selection and examination

A retrospective analysis was performed on the data of a population of children aged between 1 year and 21 years who were included in a database maintained in the Division of Pediatric Nephrology, University of Miami, Holtz Children's Hospital, between January 1996 and June 2008. An initial cohort was composed of 285 children with data collected in an investigation to profile proteinuria in a pediatric population [25]. A second cohort consisted of 27 infants who had been referred for neonatal AKI and were followed in the renal clinic for chronic kidney injury. The study was approved by the institutional review board, and all subjects were assured of anonymity in compliance with the Health Insurance Portability and Accountability Act (HIPAA).

In all, 80 children with non-diabetic kidney disease and proteinuria were identified for inclusion in this study. Patients were excluded if they had orthostatic proteinuria or any underlying systemic disease, such as diabetes, systemic lupus erythematosus, human immunodeficiency virus infection, sickle cell disease or membranous nephropathy identified by serology or kidney biopsy. They were also excluded if they had been treated with corticosteroids for the nephrotic syndrome and had shown clinical response to therapy by a significant decrease in proteinuria. The cohort was divided according to gestational age at birth, with preterm (PT) ≤32 weeks' gestation and term (T) ≥36 weeks' gestation. Size for gestational age was designated as appropriate if birth weight exceeded the 5th percentile for length of gestation [26].

Of the obese children, 22 had been born at term (Obese-T) and 22 had been born preterm (Obese-PT). A non-obese cohort of 17 patients born at term with steroid-resistant nephrotic syndrome and focal glomerular sclerosis by renal biopsy (NO-FSGS) was selected to serve as a reference group for disease progression and histomorphometry. Similarly, 19 non-obese patients born preterm (NO-PT) who had been followed longitudinally after recovery from neonatal AKI served as controls to the Obese-PT group.

Body mass index [BMI = weight (in kilograms)/height^2 (meters squared)] was recorded at each encounter as percentile values for age and standard deviation scores (SDSs) from the reference population [26]. Obesity was considered to be ≥95th percentile for gender and height and/or a z-score ≥1.65 SDS [1, 26, 27].

Casual sitting systolic and diastolic blood pressures were measured by the Dinamap® oscillometric technique at each clinic visit. Reference values were taken from the Fourth Report of the Working Group on Pediatric Hypertension [28].

Socio-economic assessment

An estimate of socio-economic status (SES) was obtained by the percent of individuals living below the poverty level in the postal ZIP code area of each patient's address as defined by the 2000 United States Census [29]. With the national average of 12.4% for individuals living below poverty level, a ZIP code with >20% was considered a high poverty environment for the purposes of this study.

Renal function and proteinuria

Twenty-four hour and/or random urine samples for protein/creatinine (Upr/cr) and microalbumin/creatinine (Ualb/cr) ratios, levels of serum creatinine and serum albumin, and blood pressures were recorded at the time of first encounter. A Upr/cr <0.2 and Ualb/cr <0.03 were considered to be normal. A Upr/cr > 2.0 and Ualb/cr>1.0 were considered to be within the nephrotic range. Estimated glomerular filtration rate (eGFR) in milliliters per minute per 1.73 m^2 body surface area was calculated by the Schwartz height index formula [30]. For the purpose of calculating renal survival, we set renal death at stage 5 chronic kidney disease (CKD) when eGFR≤15 ml/min per 1.73 m^2. Urine and serum were assayed in the central hospital clinical laboratory on a multi-channel analyzer or by Quest® referral laboratories.

Estimation of renal mass

Renal mass and function were assessed by renal ultrasound and scintigraphy. Renal mass was estimated from the

average renal length recorded by real-time sonography using a mechanical sector scanner with a 3.5–7.5 MHz transducer positioned to image the kidney in its longest dimension. Renal lengths were measured with digital calipers on a freeze-frame image. The average renal length was compared with published population standards according to age at the time of the study to within the nearest 6 months, and the z-score was calculated [31, 32].

Insulin resistance and the metabolic syndrome

In obese patients, the degree of insulin resistance was determined by the homeostatic model assessment (HOMA-IR), calculated as (fasting concentration of glucose in millimoles per liter) × fasting concentration of insulin in milliunits per liter divided by 22.5 [33]. Serum lipids were measured from blood drawn under fasting conditions and included total cholesterol, triglycerides, high density lipoprotein (HDL) and calculated low density lipoprotein (LDL).

The children in our study were classified as having the metabolic syndrome if they met three or more of the following criteria for age and gender: a BMI >95th percentile (z-score ≥1.65), a fasting concentration of glucose ≥100 mg/dl, a total concentration of cholesterol ≥130 mg/dl, a triglyceride level ≥150 mg/dl, an HDL level ≤50 mg/dl, systolic or diastolic blood pressure (BP) ≥ 95th percentile [28].

Renal biopsy and histomorphometry

Renal tissue for morphologic diagnosis was available from 23 obese patients (nine Obese-PT; 14 Obese-T) and all 17 NO-FSGS patients by light microscopy. Histomorphometry was performed by random selection from 17 (six Obese-PT; four Obese-T; seven NO-FSGS) available specimens. Computer-assisted morphometry was performed with an Olympus BH-2® microscope and MetaMorph® imaging system from Universal Imaging Corporation (http://www.universal-imaging.com). Microscopic sections were stained with hematoxylin and eosin, periodic acid–Schiff (PAS), Jones' methenamine silver, and trichrome stains. The PAS-stained slides were used for computer-assisted morphometry. We determined the average dimensions of glomerular area (GA), expressed as micrometers squared × 10^3 of mesangial tuft area, by photographing with the ×40 lens. Glomerular volume (GV) (micrometers cubed×10^6) was calculated from the glomerular area according to the formula of Weibel and Gomez as follows: $GV=GA^{1.5}\times\beta/\kappa$, where β is the shape coefficient of 1.38 and κ is 1.01, the size distribution coefficient of 10% for the variation in glomerular size for a single biopsy specimen [34, 35]. To control for observer bias, the pathologist was unaware of the patient source of the specimen.

Statistical methods

All data sets were analyzed for Gaussian distribution with the D'Agostino–Pearson omnibus test for normality. All results were expressed as the mean ± standard deviation (SD). Intergroup comparisons were analyzed by one-way analysis of variance (ANOVA) using the Tukey–Kramer multiple-comparisons test. Differences between two groups were analyzed by Student's *t*-test. Actuarial renal survival was analyzed by the Kaplan–Meier method with comparison of curves by log-rank test. Multiple regression analysis of survival curves between groups was analyzed by proportional hazards regression with calculation of hazards ratios (HR) and 95% CI. Univariate correlations were performed with Pearson's correlation coefficient (*r*). Proportional differences were tested with Fisher's exact test. Values of $P<0.05$ were considered significant.

Results

Demographics and anthropometrics

Demographic characteristics of the obese and non-obese patients according to birth weight are shown in Table 1. The majority of preterm patients (39/41=95%) had been of extremely low birth weight (<1,000 g). Of the Obese-PT, only three (14%) had been SGA. Of the 19 NO-PT patients, one had been SGA. Each patient group had an African American (AA) and Hispanic (H) ethnic predominance, with AAs composing 51% of the entire cohort.

The average percent poverty for each group exceeded the national average of 12.4% and was not significantly different between the groups (Table 1). Those of African American ethnicity had an odds ratio of 4.2 (95% CI 1.6–11.1; $P<0.01$) of living in an area of increased poverty when compared with those of Hispanic or white ethnicity. However, no other medical demographic characteristics in this cohort were significantly different, including the presence of obesity, preterm birth or progression to ESKD.

Anthropometric indices by SDSs, including weight, height and BMI, were compared. Obese-T children had significantly greater weight SDSs (2.2±0.7 versus 1.2±1.0), height SDS (0.5±1.3 versus −1.0±2.2) and BMI SDS (3.8±1.8 versus 2.3±1.0) than the Obese-PT children, respectively ($P<0.001$). The body habitus for the Obese-PT was disproportionately short and obese, while the

Table 1 Patients' demographic characteristics and clinical pathologic comparisons between obese and non-obese children with proteinuria kidney disease (*NS* not significant)

Variable	Preterm (PT)		Term (T)		ANOVA *P* value
	Obese-PT	NO-PT	Obese-T	NO-FSGS	
	n=22	*n*=19	*n*=22	*n*=17	
Gender (male) (% male)	8 (36%)	12 (63%)	11 (50%)	9 (53%)	NS
Ethnicity (%)					
African American	10 (45%)	11 (59%)	11 (50%)	9 (53%)	NS
Hispanic	9 (41%)	6 (32%)	8 (36%)	5 (29%)	NS
Caucasian	3 (14%)	2 (11%)	3 (14%)	3 (18%)	NS
Individuals below the poverty level by ZIP code (%)	20.1±12.6	21.0±10.8	16.3±9.5	16.6±10.7	NS
Birth weight (kg)	0.9±0.4[a]	0.7±0.1[a]	3.3±0.5	3.1±0.4	<0.0001
Gestational age (weeks)	28±2[a]	25±2[a]	38±2	37±3	<0.0001
BMI SDS	2.3±1.0[b]	-0.3±1.1	3.8±1.8[a]	0.2±0.5	<0.0001
eGFR (ml/min per 1.73 m^2)	67±49[a]	110±33	93±55	107±46	0.015
Proteinuria (Upr/cr) (mg/mg)	4.9±4.6[b]	0.2±0.2	3.0±3.3	10.2±9.4[a]	<0.0001
Albuminuria (Ualb/cr) (mg/mg)	2.4±3.5	0.02±0.03[a]	2.3±2.2	4.8±4.4	0.001
% Albuminuria	52±27	9±12[a]	72±21	68±21	<0.0001
Serum albumin (mg/dl)	3.9±0.8	4.5±0.4	4.0±0.5	2.0±0.9[a]	<0.0001
Average kidney length SDS	−1.2±3.0	−1.8±1.1[c]	0.0±3.1	0.7±0.1	<0.001

[a] $P<0.01$. Different from all other groups
[b] $P<0.01$. Different from NO-PT and NO-FSGS
[c] $P<0.01$. Different from Obese-T and NO-FSGS

anthropometric characteristics of the Obese-T described a more proportionate habitus as tall and heavy.

Radiological and functional evaluation of renal mass

On final renal sonography and scintigraphy, 16/41 (39%) preterm (eight obese and eight non-obese) patients exhibited at least one small and/or hypofunctioning renal unit compared to 5/39 (13%) of term patients (odds ratio 4.7; $P<0.006$). Of the preterm patients, all had had normal sized renal units at birth and most had had documented vascular thrombosis in the newborn period to explain the discrepancy in size and function in later life. Among the term patients, only the obese patients with kidney disease were found to have unilateral renal hypoplasia (four) and agenesis (one).

Average renal length was recorded at 7±4 years in the preterm patients and 11±5 years of age in the term patients. When the z-score for the average length of both kidneys was calculated, the NO-PT patients had significantly less renal tissue than those patients born at term (Table 1). In the entire cohort, renal length SDS correlated significantly to patient height SDS (r=0.4; $P<0.01$), consistent with the reference population [32].

Clinical course and progression of kidney disease

Average longitudinal follow-up for the entire cohort was 7.4 ±4 years. The group followed the longest was the NO-PT at 10±4 years, since they had been identified at birth. The shortest follow-up was in the Obese-T group at 5±4 years. Of the Obese-T patients, 5/9 (56%) presented with ESKD without prior diagnosis. The remainder presented with asymptomatic proteinuria and hypertension. As in the Obese-T patients, the Obese-PT patients tended to present with fewer symptoms and an inordinate decrease in eGFR.

Twenty-six preterm infants (seven Obese-PT and 19 NO-PT) were followed since birth and had neonatal AKI documented by peak levels of serum creatinine averaging 2.9±1.0 mg/dl (range 1.5-5.3 mg/dl), which had decreased to an average of 0.6±0.4 mg/dl (range 0.3-1.9 mg/dl) by 6 months of age. The differences between the obese and non-obese preterm were not significant ($P=0.07$).

Absolute total proteinuria and albuminuria was greater in the NO-FSGS patients with steroid-resistant nephrotic syndrome (Table 1). Despite heavy proteinuria, the obese groups maintained normal levels of serum albumin and manifested no edema, while the NO-FSGS had significantly lower serum albumin levels and symptomatic edema. There was a significant negative correlation between total proteinuria and eGFR (r=−0.5; $P<0.001$) in the obese patients. Increasing albuminuria also correlated with loss in kidney function, although the relationship was less significant (r=−0.4; $P<0.05$).

Treatment with angiotensin-converting enzyme inhibitors (ACEIs) and/or angiotensin receptor blockers (ARBs) was prevalent in the NO-FSGS control group 13/17 (76%) and the

Obese-T group (6/22=27%) but rare in the preterm patients (Obese-PT 3/22=14%; NO-PT 2/19=11%). No effect of these therapies was apparent in the renal outcome of any group.

Insulin resistance and the metabolic syndrome

Insulin resistance and components of the metabolic syndrome are shown in Table 2.

Average age at the time of examination for insulin resistance and the metabolic syndrome for the obese patients was 11.9±4.9 years. Overall, 38/44 (86%) of the obese children met criteria for the metabolic syndrome, with an average score of 4±1. In the Obese-PT group 20/22 (91%) met three or more criteria for the metabolic syndrome compared with 18/22 (82%) of the Obese-T (P=1.0). Obese patients had similar measures of insulin resistance as measured by HOMA-IR (Table 2). Dyslipidemia was prominent in obese children and was characterized by increased levels of total cholesterol and serum triglycerides as well as low HDL.

Renal survival relative to birth weight

Figure 1 demonstrates the actuarial renal survival curves for the four groups of patients with a significant difference by log rank test (P=0.02). The median renal survival was 23 years in the Obese-T, 16 years in the NO-FSGS, and 15 years for the Obese-PT. None of the NO-PT patients showed progression to ESKD, although 6/19 (32%) had CKD with decreased eGFR <90 ml/min per 1.73 m^2. Obese-PT patients showed increased risk of renal death during childhood compared with Obese-T (HR=2.4; 95% CI=1.1 to 7.1; P=0.04) and NO-PT (P<0.005) patients. There was also a trend for improved survival in the Obese-T compared with the NO-FSGS patients (HR=0.4; 95% CI=0.1 to 1.0; P=0.06).

Table 2 Components of the metabolic syndrome in obese children with kidney disease (*NS* not significant, *SBP* systolic blood pressure, *DBP* diastolic blood pressure)

Variable	Obese-PT	Obese-T	Preterm versus term
	n=22	n=22	
Gender (male:female) (% male)	8:14 (36%)	11:11 (50%)	NS
Age at presentation (years)	6±5	12±4	<0.0001
BMI (kg/m^2)	25±5	33±8	<0.001
BMI (z-score)	2.3±1.0	3.8±1.8	0.001
HOMA-IR	4.5±2.3	6.4±4.8	NS
Fasting level of glucose (mg/dl)	90±16	85±10	NS
Fasting level of insulin (uU/ml)	21±10	31±23	NS
Total cholesterol level (mg/dl)	203±67	202±56	NS
Triglyceride levels (mg/dl)	306±467	186±94	NS
HDL (mg/dl)	45±10	43±12	NS
LDL (mg/dl)	125±59	122±56	NS
SBP (Percentile)	89±18	76±25	NS
≥95th percentile, number (%)	12 (55%)	8 (36%)	NS
DBP (percentile)	78±23	66±23	NS
≥95th percentile, number (%)	8 (36%)	3 (14%)	NS

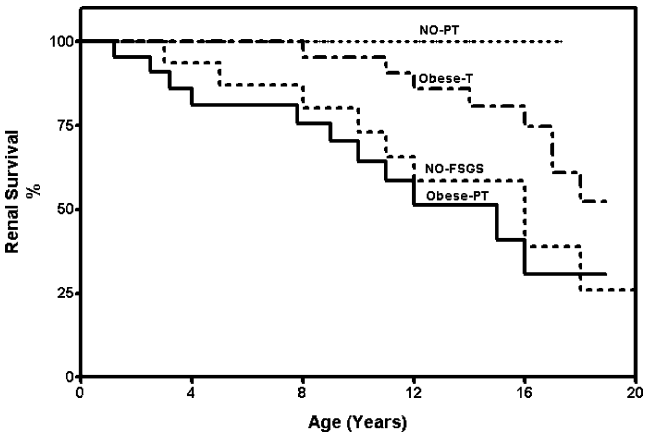

Fig. 1 Kaplan–Meier actuarial renal survival curves in four groups of children with kidney disease. Obese-PT patients had increased risk of renal demise during childhood compared with Obese-T (hazard ratio 2.4; 95% CI 1.1 to 7.1 P=0.04) with median renal survival of 15 years of age for Obese-PT compared with 23 years for Obese-T patients

Renal pathology and histomorphometry

All Obese-PT who had renal pathologic diagnoses (9/22) showed findings consistent with FSGS. Of the 14 Obese-T patients who underwent renal biopsies, 12 showed FSGS and two showed mesangial proliferation.

Histomorphometry was performed on ten obese (six O-PT; four Obese-T) and seven NO-FSGS renal tissue specimens. An average of 9.6±8 glomeruli were measured from each biopsy specimen. An average of 86±56 (range 56–106) glomeruli from each group were measured for glomerular tuft area. Glomerulomegaly as measured by glomerular volume was similar in the obese children, regardless of birth weight (Obese-PT 38.3±12.6 $\mu m^3 \times 10^6$ versus Obese-T 42.0±7.0 $\mu m^3 \times 10^6$), but was significantly greater than that of the NO-FSGS patients (22.6±7.0 $\mu m^3 \times 10^6$; P<0.01) (Fig. 2a).

Figure 2b shows the pathologic comparison on renal biopsy of glomeruli from a non-obese patient with FSGS compared with those from obese patients of normal and low birth weight. This composite provides the histologic picture demonstrating the morphometric measurements.

Discussion

This study brought insight into a growing population of children with obesity-related kidney disease, especially in

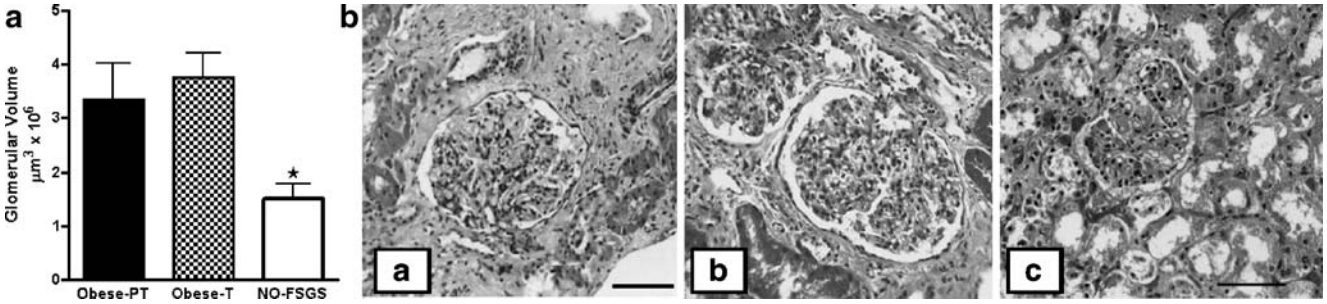

Fig. 2 **a** Graphic comparison of average glomerular volume ($\mu m^3 \times 10^6$) by histomorphometry in Obese-PT, Obese-T and NO-FSGS patients. Average glomerular volume was similar in obese patients (Obese-T and Obese-PT), regardless of birth weight, but was significantly less in non-obese patients (NO-FSGS); **P*=0.008 by ANOVA. **b** Composite photomicrograph. *A* Obese patient born preterm of low birth weight presenting with proteinuria. The glomerulus is larger than that of the non-obese control, and there is extensive peri-glomerular and interstitial fibrosis. *B* Obese patient of normal birth weight presenting with heavy proteinuria. The glomerulus is larger than that of the control. *C* Age-matched non-obese control with FSGS. Observe a normal-sized glomerulus. Hematoxylin and eosin, ×200. Internal scales 100 μm

those born preterm. The lesion of glomerulomegaly, focal and global sclerosis and a more insidious progression to renal failure compared with that in non-obese patients with FSGS has characterized ORG in adults [2–4]. In our cohort of obese children, the pathologic finding of FSGS was the predominant lesion in both groups of obese children, regardless of birth weight. The clinical course in the obese children born at term was typical of the ORG described in adults and adolescents [4, 5] with a protracted course in comparison with that in patients with typical FSGS [3]. In distinction, the condition of obese preterm children deteriorated more rapidly, although their presentation was also characterized by lack of edema and normal serum levels of proteins. A recent report of six adult patients born preterm who developed secondary FSGS provided observations similar to our own, with the caveat that obesity seemed to accelerate the pathogenesis in children [36].

The greatest limitation in this retrospective observational study was the identification of a suitable control group to compare with the preterm obese patients. The longitudinal database at our institution of preterm infants with evidence of chronic kidney injury allowed such a comparison. The demographic characteristics of our cohort were also important, in that ethnic differences might impose an important bias. Despite a 57% Hispanic ethnic predominance in South Florida, African American children composed the majority of our cohort and were more likely to be living in poverty. These disparate characteristics may account for the seemingly large number of patients with obesity, preterm birth and renal disease at this urban medical center.

Previous studies have demonstrated increased blood pressure, salt sensitivity, reduced renal mass, and microalbuminuria in adults born preterm, whether small or appropriate for gestational age [37–39]. Our data support these findings in our preterm patients with kidney disease. Not surprisingly, all the preterm patients showed evidence of significantly smaller renal mass than a reference population and the term patients. Although hypertension and loss of renal mass were common in the non-obese preterm patients, renal function was well preserved and proteinuria was minimal.

Proteinuria as a consequence and perpetrator of renal injury is evident in this and other studies of CKD [2, 5, 15, 19, 25]. The relationship of increasing proteinuria with loss in eGFR was shown in our observations and confirms that of numerous other reports in adults and children [2, 15–17, 19, 25]. An interesting observation, that many of the obese patients had normal levels of serum albumin in the face of heavy proteinuria, may be related to the character of their proteinuria. We have shown previously that the albumin component of proteinuria may be less in children, especially in those of younger age with primarily tubular disease [19]. The mechanisms by which obesity imposes systemic and local cytochemical reactions may also result in a predominance of non-albumin proteinuria which would maintain normal serum proteins until the terminal phases of the disease [23].

In the cohort described here, glomerulomegaly was present and similar in the obese patients, regardless of birth weight, when compared with the non-obese FSGS controls. Glomerulomegaly as a component of obesity-related renal disease has been described in a large number of adults [3]. Total kidney specimens are necessary for the measurement of glomerular number, but histomorphometry by biopsy sampling can give important data regarding glomerulomegaly and suspected glomerular hypertension [3, 7–10, 32]. Some reports indicate that obesity or increased BMI alone may be an independent initiator of glomerular hypertension by various systemic and local mechanisms included in the cascade towards focal glomerulosclerosis [6–10, 23]. Of interest is that there was no apparent difference in glomerulomegaly according to birth weight, suggesting that

obesity was the primary offender. This association requires further investigation.

We have previously observed in preterm infants that overweight at 3 years of age resulted in a more rapid progression to renal demise [19]. Preterm birth, regardless of size for gestational age, appears to be a cause of low nephron endowment, since active nephrogenesis is ongoing in utero until 36 weeks' gestation. After preterm birth, glomerulogenesis ceases within approximately 40 days, and fewer glomeruli are produced in proportion to the length of gestation [12]. Reduced renal mass, whether by acquired renal disease, nephrectomy, ischemic injury, or congenital oligonephronia, may be a major vulnerability factor in progression of kidney disease [2, 6, 7]. Our data indicate that, in obese children born preterm, kidney disease was two-times more likely to advance to ESKD than in obese patients born at term and five-times more likely to progress than in non-obese preterm children. This finding supports the need for prospective cohort studies in this population in an effort to decipher the relative role of ischemic nephropathy versus preterm birth on nephron endowment.

The metabolic syndrome is recognized as a syndrome complex of insulin resistance and dyslipidemia, aggravated by central obesity [23, 24, 33]. It is increasingly described in association with the genetic predisposition to type 2 diabetes and is believed to have its origins in "developmental programming" or the fetal origins of adult disease [14, 22]. All our obese pediatric patients had similar markers of the metabolic syndrome, including significant insulin resistance, compared with a general pediatric population without renal disease [24]. Preterm birth and rapid weight gain during the first years of life are associated with early insulin resistance and hypertension in childhood and adolescence, regardless of size for gestational age [13, 20–22, 37–39].

In summary, obesity is an important modifiable risk factor in the development and progression of renal disease in children, especially those born preterm, whether appropriate or small for gestational age. Individuals of extreme prematurity will have proportionately less nephron mass and, with their improved survival, may emerge as an important population at risk for renal disease progression. If they have genetic predisposition to renal disease, their risk becomes more significant. It is particularly important that we study infants and children in an attempt to recognize those critical windows during early life in which programming of adult diseases occurs. Ultimately, these may become the potential windows for therapeutic interventions aimed to prevent late onset of disease.

Acknowledgments This study was supported in part by a grant from Florida's Department of Health, Children's Medical Services.

The authors have no conflict of interests referable to the content of the manuscript or financial interest in any of the products or procedures mentioned.

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