Female Adolescents with Chronic or End-Stage Kidney Disease and Strategies for their Care

Maria E. Diaz-Gonzalez De Ferris, MD, MPH, PhD,[*,‖] Ana Catalina Alvarez-Elías, MD, MS,[†,‖] Michael Ted Ferris, BA,[‡,‖] and Mara Medeiros, MD, PhD[†,§,‖]

Summary: The prevalence of chronic or end-stage kidney disease in pediatric girls is lower than in boys, however, girls have unique morbidities that can have great effect on their quality of life. For female adolescents, creatinine excretion peaks at approximately 14 years of age and is significantly less than males, owing to lower muscle mass. Females have higher nitric oxide activity, and estrogens may contribute to lower blood pressure. Females excrete less growth hormone during the prepubertal and pubertal years. Females between the ages of 8 and 10 years show increased levels of parathyroid hormone and vitamin D, however, female adolescents with chronic kidney disease have less estrogen and loss of the luteinizing hormone pulsatile pattern. These biological, hormonal, and physical changes affect the psychosocial aspects of female adolescents with chronic kidney disease/end-stage kidney disease, and they must learn to manage their health to achieve good outcomes. Patients and their parents must learn disease management through a customized health care transition preparation in both the pediatric- and adult-focused settings. Clinical strategies are suggested for the care of these special patients.
Semin Nephrol 37:320-326 © 2017 Published by Elsevier Inc.
Keywords: Adolescents, females, chronic kidney disease, end-stage kidney disease, health care transition, self-management

Adolescents and young adults with chronic kidney disease (CKD) or end-stage kidney disease (ESKD) have unique morbidities as a result of their physical and psychological changes. Adolescents and young adults account for less than 5% of all of the ESKD population, but have a 10-year survival rate of 70% to 85%.[1–4] Despite this high survival rate, their mortality rate still is 30 times higher than their healthy peers, mainly owing to cardiovascular disease or infection.[2] Transplant recipients have significantly higher survival rates than patients on dialysis alone.[4] Socioeconomic status and racial disparities are apparent in CKD.[5]

Adolescents with CKD and ESKD experience the physical and psychological demands of puberty while having to learn to self-manage their comorbidities (Table 1). In this review, we focus on the female adolescent with CKD/ESKD, highlighting targeted areas of intervention to improve outcomes (Table 2).

ADOLESCENT CKD AND ITS ETIOLOGY

The prevalence of CKD in adolescents is unknown. In the United States Renal Disease Study, there are more males than females in all pediatric age groups. The etiology of CKD related to congenital anomalies of the kidneys and urinary tract accounts for 73% in the 0 to 1-year age group, and diminishes to 38.7% in adolescents older than 12 years of age,[1] whereas glomerular diseases and focal segmental glomerulosclerosis account for one third of patients older than 12 years of age.[1] In adolescents and the young adult population with ESKD, there are more males than females as per the registry of the European Society of Pediatric Nephrology/European Renal Association−European Dialysis and Transplant Association of 2016, which includes more than 1,000 patients from 36 European countries.[3] They report a frequency of ESKD in 61% of males with the leading cause of ESKD being the Congenital Anomalies of Kidney and Urinary tract, with less favorable outcomes in black and Asian patients.[3] The reasons for these differences in outcomes in minority populations may be multi-factorial. There is a higher prevalence of poverty among African Americans compared with whites, and focal segmental glomerulosclerosis is approximately 4 times more common in adolescent African Americans compared with other races (35.0% versus 9.0%).[5] In developing countries, chronic glomerulonephritis is the main known cause of CKD/ESKD, which may be due to the high prevalence of infections.[2]

ADOLESCENT RENAL PHYSIOLOGY AND HYPERTENSION

The differences in normal adolescent renal physiology by sex remain under investigation, but in animal

[*]*Department of Pediatrics, The University of North Carolina School of Medicine, Chapel Hill, NC, USA.*
[†]*Department of Pediatric Nephrology, Nephrology Research Laboratory, Hospital Infantil de México Federico Gómez, Mexico City, DF, Mexico.*
[‡]*Simione Consultants, Hamden, CT, USA.*
[§]*Nephrology Research Laboratory, Hospital Infantil de México Federico Gómez, Mexico City, DF, Mexico.*
[‖]*Department of Pharmacology, Faculty of Medicine, National Autonomous University of Mexico.*

Financial disclosure and conflict of interest statements: none.
Address reprint requests to Maria E. Diaz-Gonzalez De Ferris, MD, MPH, PhD, Department of Pediatrics, The University of North Carolina at Chapel Hill. E-mail: maria_ferris@med.unc.edu

0270-9295/ - see front matter

http://dx.doi.org/10.1016/j.semnephrol.2017.05.003

Table 1. Female Adolescents With Kidney Disease

Characteristic	Females Compared With Males
Most common CKD etiology	Younger adolescents: congenital anomalies of the kidney and urinary tract Older adolescents: glomerular conditions
Renal physiology and hypertension (mostly animal models)	AQP1 expression is lower in female rats and up-regulated moderately by progesterone This may explain the clinical differences in blood pressure by sex Higher nitric oxide activity Nitric oxide synthase has greater activity in the renal inner medulla
Measures of renal function	Creatinine excretion peaks at 14 years of age Lower Cystatin C (healthy adolescents)
Growth and GH	Adult height can be reached by 18 years of age Urinary excretion peaks at age 13 Less GH during the prepubertal and pubertal years GH pulsatile amplitude peak is higher in transplanted females GH resistance (in both sexes)
Bone mineral metabolism and metabolic bone disease	Parathyroid hormone and vitamin D levels are similar between males and females during childhood, however, females between the ages of 8 and 10 years show an increase in serum levels compared with males (ages, 10-12 y) Peak bone mass is acquired during adolescence, reaching 99% at 22 $\pm$ 2.5 years in young healthy women Asian women have lower femoral neck bone mineral content during midpuberty and lower whole-body mineral content in pre-/early puberty than Caucasian females
Anemia	Lower erythropoiesis results from the lower androgen stimuli
Endocrine comorbidities	Menarche could be delayed until 16 years of age Females with CKD have less estrogen and loss of luteinizing hormone pulsatile pattern
Psychosocial aspects of CKD	CKD affects quality of life Treatment burden (number of medications) increase as CKD progresses Nonadherence is a major issue in these patients
Cognition and quality of life in CKD	Younger age at diagnosis is a risk for cognitive impairment, in executive functions and high-level cognitive tasks Children with CKD have a lower QOL and greater depression than their healthy peers, not associated with GFR, but with disease duration Higher maternal education is associated with higher physical, social, and school QOL
Family aspects of pediatric CKD	Families of children with CKD undergo great psychosocial, emotional, and economic stress Higher family income is associated with better blood pressure management, height deficit recovery, and slower disease progression
Self-management and health care transition	Females tend to perform at a slightly higher level of self-management and health care transition readiness

AQP, aquaporin; GH, growth hormone.

models, sexual hormones have been described as the main influence in these differences. Herak-Kramberger et al[6] found that aquaporin 1 expression is lower in female rats and up-regulated moderately by progesterone. This may explain the clinical differences in blood pressure by sex.

Ojeda et al[7] showed the contribution of estrogens in the normalization of blood pressure in an animal model with fetal programmed hypertension. By inducing placental insufficiency in ovarectomized rats and intrauterine growth restriction, hypertension developed, but diminished significantly with the application of estrogens.[7] Nitric oxide synthase has greater activity in the renal inner medulla in female rats mediated by sex hormones. Blood pressure increases based on nitric oxide synthase activity in spontaneously hypertensive rats.[8] Adolescents have lower plasma renin and angiotensin II levels and have a circadian sodium excretion associated with a peak of atrial natriuretic peptide at midnight. There is also an increase in renin and angiotensin II with a decrease in sodium excretion owing to increased sodium reabsorption at night.[9] In a US cohort of CKD patients (stages 1-4) with a median age of 11 years, hypertension or stroke was reported in 29% as compared with 19% of children in the National Health and Nutrition Examination Survey study with a BMI greater than the 90th percentile for age.[10]

MEASURES OF RENAL FUNCTION IN ADOLESCENCE

Creatinine excretion peaks at approximately 15 years of age in males and at approximately 14 years of age in females. Males excrete a significantly higher amount than females because of greater muscle mass. The increase in height during puberty also leads to a maximum albumin excretion.[11] Cystatin C is lower