Adolescent onset glomerular disease outcomes, the clinical and social implications

KELLY GARRITY, MD

2ND YEAR UCLA PEDIATRIC NEPHROLOGY FELLOW

KGARRITY@MEDNET.UCLA.EDU

NATHANIEL PUTNAM, MS; DEBBIE GIPSON, MD; ELOISE SALMON, MD (UNIVERSITY OF MICHIGAN); ELAINE KAMIL, MD(CEDAR SINAI); SUSAN MASSENGILL, MD (ATRIUM HEALTH); JAYA ISSAC, MD (MONTEFIORE); MYDA KHALID, MD (IU)

Background

- Many studies look specifically at adult or childhood onset glomerular disease, but few studies look specifically at adolescent onset glomerular disease
  - ~75% of childhood nephrotic syndrome is due to Minimal Change Disease
  - FSGS is the more common presentation in adolescents
- While many studies aggregate adolescent onset disease into childhood onset studies, there are data to suggest that adolescent onset glomerular disease may have a different phenotype and different disease trajectory
  - Prior studies showed patients with IgA nephropathy, FSGS, and membranous nephropathy all had better outcomes if onset occurred earlier in childhood compared to adolescence

Background

- Limited research exists regarding the social outcomes of adolescent onset glomerular disease and on glomerular disease as a whole
- Studies looking at pregnancy rates in female dialysis patients show these women are up to 40x less likely to become pregnant than women off dialysis
  - Studies show low likelihood of women on dialysis being able to achieve pregnancy who are actively pursuing such
- Studies on male patients on dialysis show abnormalities to the morphology, speed, number, and concentration of sperm

Aims

To define the social and clinical outcomes of adolescent onset glomerular disease

To compare the social and clinical outcomes of adolescent onset glomerular disease with outcomes in other glomerular disease onset age groups in the CureGN database

CureGN

- CureGN is a multi-center, prospective observational cohort study of patients with glomerular disease funded by the NIH-NIDDK.
  - Enrolls children and adults with biopsy-proven minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MN), or IgA nephropathy/vasculitis (IgAN/IgAV) from the USA, Canada, Italy, and Poland

Objectives

1. Understand that glomerular disease has a significant impact on educational attainment
2. Realize that glomerular disease may impact women's likelihood of a successful live birth
3. Understand that socioeconomic status impacts likelihood of progression to end stage kidney disease in patients with glomerular disease
4. Understand the impact of APOL1 status on likelihood of achieving prolonged sustained remission of kidney disease off treatment

Population/Comparison Cohort

- Population of interest: CureGN participants between ages 13 to 19 at the time of disease presentation or biopsy, whichever came first
- Comparison cohorts: CureGN participants between ages 5-12, 20-29, and 30-39 at the time of disease presentation or biopsy, again whichever came first

Patient Demographics and Characteristics

	Age at Diagnosis (years)			
	5-12 (N=267)	13-19 (N=351)	20-29 (N=281)	30-39 (N=326)
Male	167 (63%)	209 (60%)	144 (51%)	184 (56%)
Age at most recent visit	10 (8, 12)	20 (18, 22)	30 (27, 33)	40 (37, 43)
Race				
Asian	16 (6%)	10 (3%)	40 (14%)	42 (13%)
Black/African American	39 (15%)	76 (22%)	44 (16%)	43 (13%)
White	187 (70%)	241 (69%)	171 (61%)	212 (65%)
Other	25 (9%)	24 (7%)	26 (9%)	29 (9%)
Diagnosis				
MCD	161	68	51	41
FSGS	70	110	84	92
MN	5	37	40	79
IgAN	31	136	106	114
Time since Biopsy, yrs	6.6 (4.6, 8.4)	5.1 (3.4, 6.8)	5.4 (3.0, 7.5)	5.4 (3.4, 7.6)
CureGN Observation, yrs	4.9 (3.3, 6.4)	4.2 (1.8, 5.5)	4.1 (1.7, 5.9)	4.1 (1.7, 5.7)

Continuous variables reported as Median (25^{th}, 75^{th} percentile)

Social Outcomes

- Descriptive Statistics on:
  - Occupation (Full time, part time, and no work/education)
    - Full time defined as full time employment, full time student, or part time student and part time employment
    - Part time defined as part time student or part time employment
  - Educational Attainment (less than high school, high school/GED, associates degree or higher)
  - Pregnancies

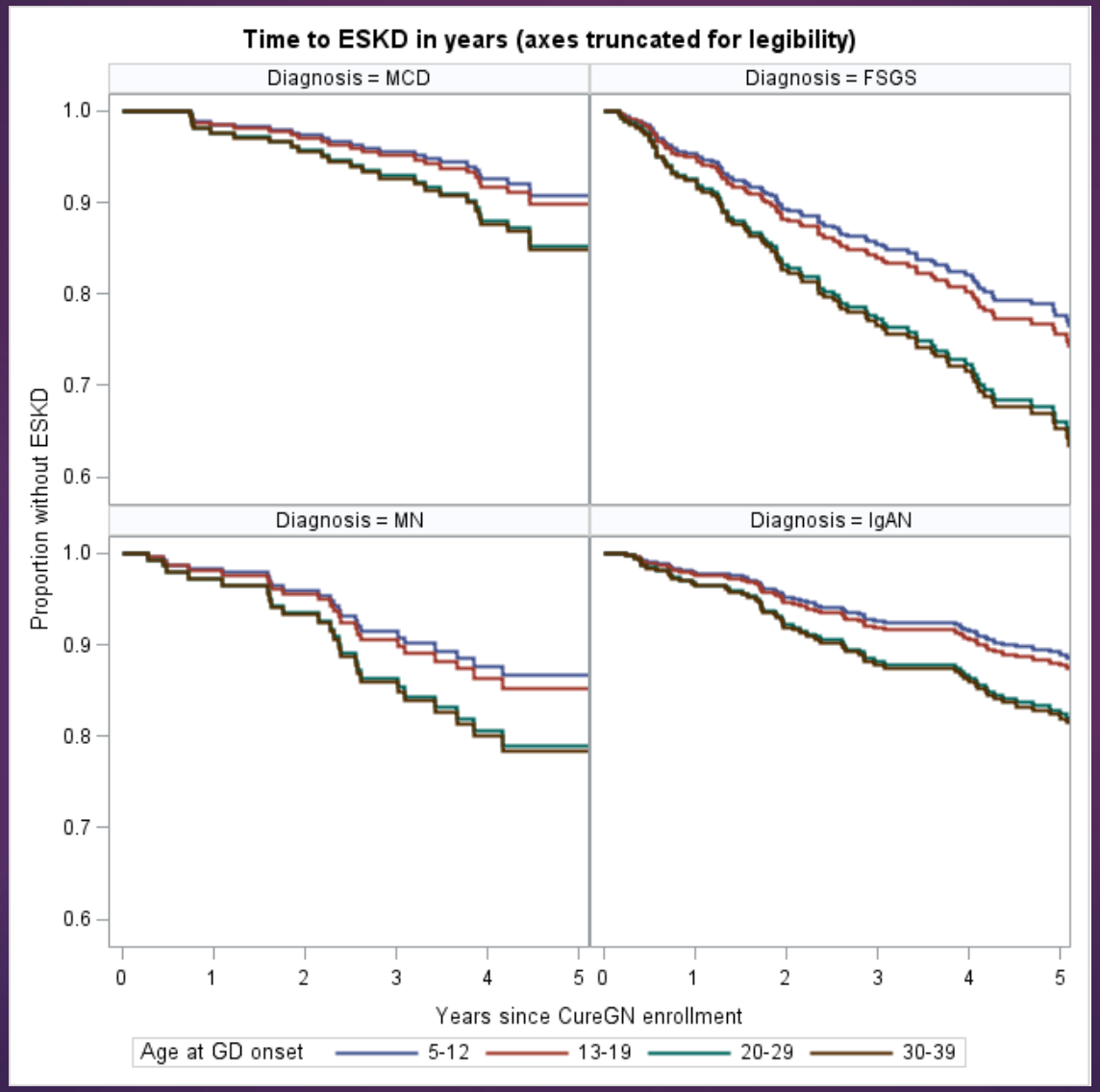
Clinical Outcomes

- Composite measure of End Stage Kidney Disease (ESKD) and/or 40% reduction in estimated glomerular filtration rate (eGFR) from baseline measured at study enrollment
  - Censored at date of last contact or death
  - 40% reduction in eGFR from baseline has been shown to predict progression to ESKD
- Sustained Complete Proteinuria Remission off Treatment (SROT)
  - SROT was defined as Urine Protein Creatinine Ratio (UPCR) <0.3 and/or urinalysis protein negative or trace for at least 1 year while not on immunosuppressive therapies with $\geq$ 75% preservation of the eGFR at the time of biopsy
  - IgAN cohort also requires urine dipstick blood negative or trace during follow up
  - Censored at the date of last contact, ESKD, or death
  - Proteinuria has been shown to hasten progression of kidney disease in all 4 glomerular diseases and blood has been shown to hasten progression in IgAN

Methods

- ESKD/40% eGFR reduction
  - Covariates: Sex, Ethnicity, Race, SES parental/self education, BP control, Adherence, Time varying obesity status, Baseline CKD stage, APOL1, # of coexisting conditions (other than HTN)
- SROT
  - Covariates: Sex, Ethnicity, Race, SES parental/self education, Adherence, BP Control, Time Varying Obesity Status, Baseline CKD stage, APOL1
- Variable of interest: age at kidney disease onset (13-19 vs all other age groups)
- Strata: kidney disease diagnosis
- Used Backwards Variable Selection for both
- Both Analyzed using Cox proportional hazard models

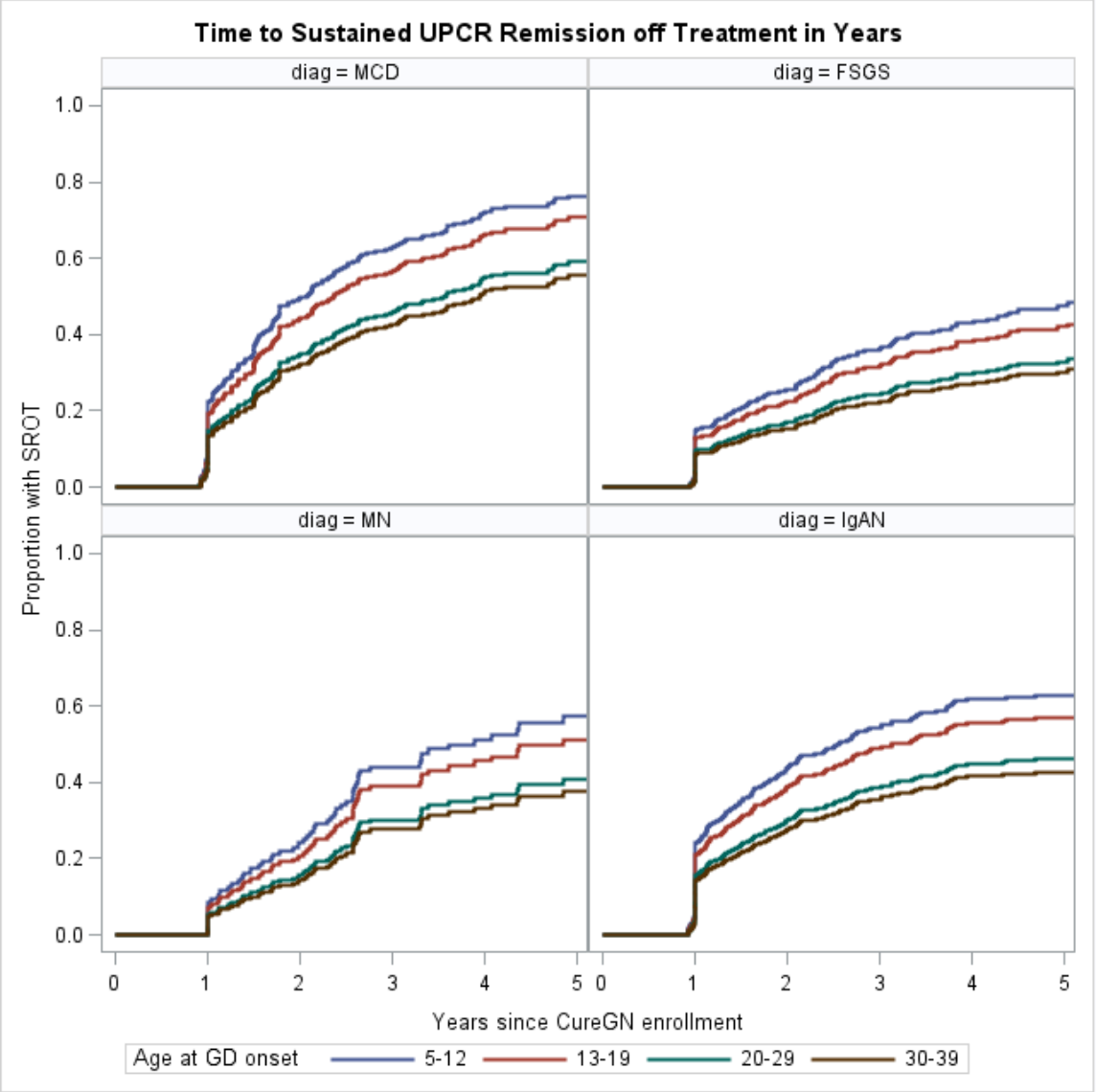
ESKD Survival by Age Group



ESKD Model	Parameter (CI)
Age At Onset (reference: 13-19)	
5-12	-0.05 (-0.48, 0.37)
20-29	0.13 (-0.30, 0.56)
30-39	0.16 (-0.26, 0.58)
Education (reference: High School)	
Less than High School	-0.34 (-0.90, 0.21)
2- or 4-year degree	-0.04 (-0.33, 0.25)
Graduate Degree	**-0.93 (-1.49, -0.37)**
EGFR at Biopsy (reference: EGFR 90+)	
EGFR 60-90	0.10 (-0.30, 0.50)
EGFR 30-60	**1.08 (0.71, 1.45)**
EGFR 15-30	**1.29 (0.73,1.85)**
EGFR <15	**1.39 (0.63, 2.14)**
Glomerular Disease Diagnosis (Reference: MCD)	
FSGS	**0.86 (0.41, 1.31)**
MN	**0.60 (0.02, 1.18)**
IgAN	0.12 (-1.05, 1.29)

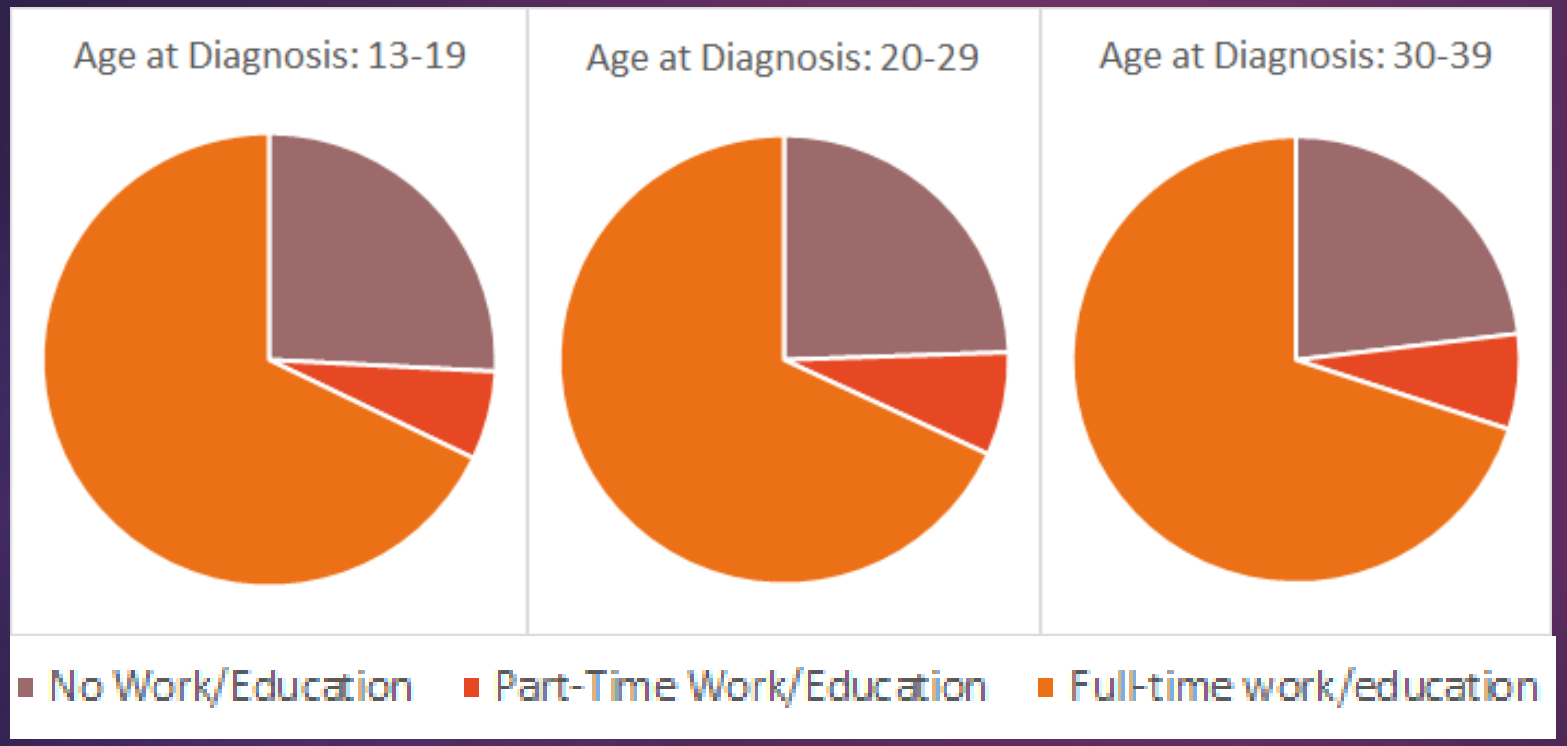
- Covariates: Sex, Ethnicity, Race, **SES parental/self education**, BP control, Adherence, Time varying obesity status, **Baseline CKD stage**, APOL1, # of coexisting conditions (other than HTN)

SROT Occurrence by Age Group



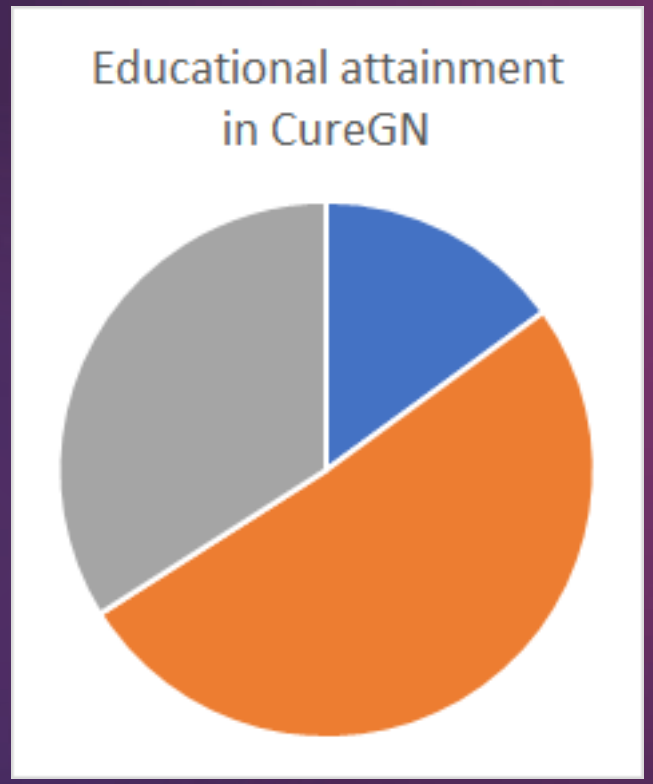
SROT Model	Parameter (CI)
Age At Onset (reference: 13-19)	
5-12	0.13 (-0.09, 0.36)
20-29	-0.26 (-0.53, 0.01)
30-39	**-0.31 (-0.59, -0.04)**
EGFR at Biopsy (reference: EGFR 90+)	
EGFR 90-60	-0.17 (-0.38, 0.05)
EGFR 30-60	**-0.67 (-0.99, -0.35)**
EGFR 15-30	-0.36 (-0.84, 0.12)
EGFR <15	-0.01 (-0.69, 0.65)
Glomerular Disease Diagnosis (Reference: MCD)	
FSGS	**-0.63 (-0.88, -0.39)**
MN	**-0.65 (-0.98, -0.32)**
IgAN	-0.19 (-0.41, 0.02)
APOL1 Risk (Reference: Low Risk)	
High Risk	**-0.73 (-1.26, -0.20)**
Unknown Risk	0.13 (-0.32, 0.07)

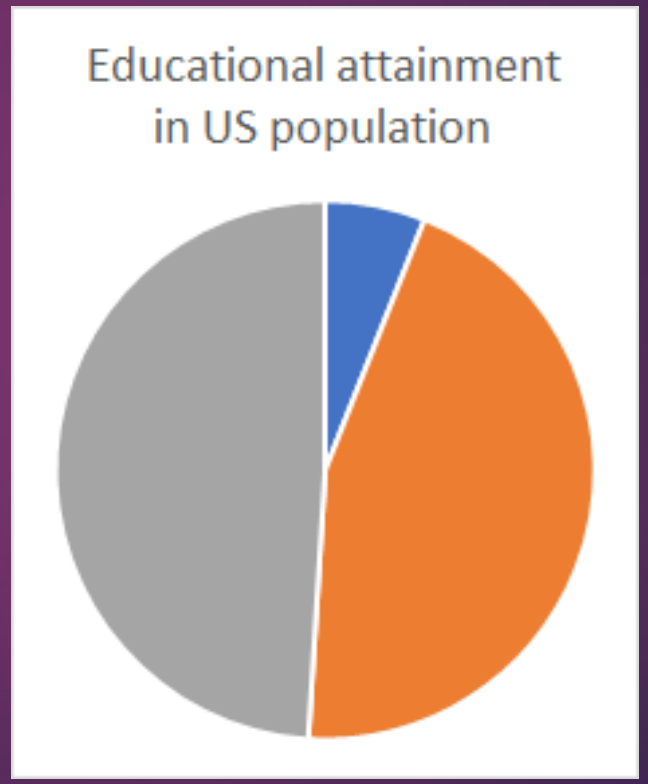
Current Employment Across Different Onset Groups



Across all onset groups, 68% of the study population currently works or studies full-time. 6% works or studies part-time, and 26% is not working or studying. This did not vary by age at diagnosis as above

Educational Attainment in CureGN and the US population





Less than High School High School Diploma Associates degree or higher

Kidney Disease

85% Earn a High School Diploma or GED

In CureGN participants with follow up between ages 18-25

34% Earn an Associates Degree or Higher

In CureGN participants with follow up between ages 27-35

General US Population

94% of the General US Population Earn a High School Diploma or GED

49% of the General US Population Earn an Associates Degree or Higher

The National Center for Education Statistics. Https://nces.ed.gov/fastfacts/display.asp?id=27

Pregnancies

- 3% of women (5 out of 142) with adolescent onset glomerular disease (median age 20, IQR 18-22) had at least one live birth, compared to 13% of women in the US population by age 19
  - only 10 post-diagnosis conceptions recorded in this group, 5 of which were live births
  - the last pregnancy recorded is at age 22, even though we follow ~20% (30 women) beyond that age (max follow up age 28)
  - Out of 110 women in the 20-29 group who had post-biopsy follow up between ages 23-28, 18 (16%) had 24 **post-biopsy** conceptions where the woman was aged 23-28, and 19 (79.2%) of them were live births
- 14% with young adult onset glomerular disease (median current age 30, IQR 27-33) had at least one live birth after their diagnosis, compared to 61% of women in the US population by age 29
  - Across 304 women in the 20-29 and 30-39 groups, 72 (24%) had 96 pregnancies pre-biopsy, with an 86.5% live birth rate

Discussion

- This is the largest study to date looking specifically at the results of adolescent onset glomerular disease
- There is no prior research looking at the impact of glomerular disease on educational attainment, our descriptive data suggests that glomerular disease negatively impacts educational attainment
- While the differences between adolescent and both young adult and adult onset glomerular disease clinical outcomes were largely not statistically significant, every single clinical outcome graph shows adolescents having worse results than those with childhood onset and better than results than those with older onset
  - We did see a significant difference in the likelihood of sustained complete proteinuria remission between adolescent and adult onset glomerular disease
  - With longer follow up and more patients it is possible these results will become statistically significant

Limitations

- Too few patients with childhood or adolescent onset Membranous Nephropathy
- Duration of follow up, ESKD status/40% decline may not be reached in a median of 4-5 years. With longer follow up more variables may prove significant
- Patients with greater means and education are more likely to enroll in a database like CureGN
- Pregnancy data doesn’t look not broken down by CKD stage at diagnosis or glomerular disease diagnosis

Conclusions

- Adolescent onset patients have a similar timeline of ESKD progression as child onset patients and better outcomes than adult onset patients, though this difference was not significant
- Adolescent onset patients show a transitionary profile of Sustained Complete Proteinuria Remission off Treatment between child onset patients and adult onset patients, with worse outcomes than child onset patients, but significantly better outcomes than adult onset patients
- Patients with glomerular disease had lower rates of High School Diploma/GED acquisition, lower rates of higher education acquisition, and fewer live births than the US general population
- Case controlled prospective studies are needed to further investigate the impact of glomerular disease on educational attainment

Conclusions pregnancy

- Studies looking at pregnancy rates in female dialysis patients show these women are up to 40x less likely to become pregnant than women off dialysis
- Studies show low likelihood of women on dialysis being able to achieve pregnancy who are actively pursuing such
- Studies on male patients on dialysis show abnormalities to the morphology, speed, number, and concentration of sperm
- Females with adolescent onset glomerular disease's conception rates were half the live birth rates of adolescents without glomerular disease, suggesting that glomerular disease does not simply impact an inability to successfully carry a pregnancy, but impacts fertility/family planning
- Further research is needed to validate these findings and if validated, determine the impact of glomerular disease on both fertility and family planning

Sources

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