Clinical Biomarker Trend in C3 Glomerulopathy

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Background

There is a paucity of data defining the natural history of the clinical and complement biomarker characteristics of C3 Glomerulopathy (C3G) patients. Whether there are disease related trends or relationships between the markers of disease is unknown. In a series of C3G patients, we sought to describe the trend of the three most commonly available markers of disease over a one year time period: complement C3, urine protein-to-creatinine ratio (UPCR), and eGFR. We hypothesized that lower C3 levels, as a reflection of ongoing complement activity would be associated with progressive renal disease – represented by changes in UPCR and /or eGFR.

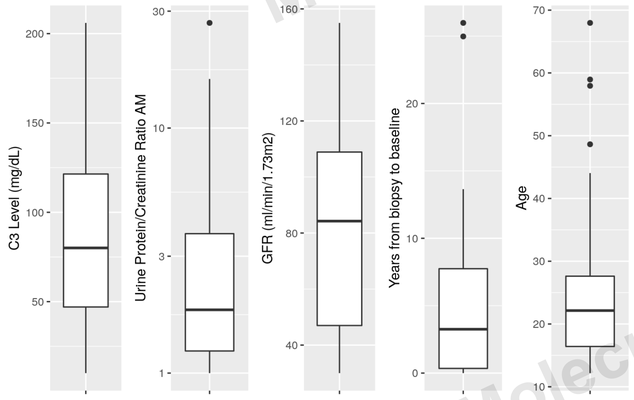
Methods

All patients met the consensus, renal biopsy definition of C3G[1]. Thirty-two subjects with an age > 12 years and GFR > 30ml/min were included. Data were analyzed in 1-year spans of data. Analyzed data included all spans for which paired C3, UPCR and GFR data were available - demarcating the beginning and end of a given span. A total of 61, one year spans were identified. Mean and median statistics across all spans were reported as percent change per year and standard regression analyses were used to define the relationship between variables

Results

Fig 1. Baseline Clinical Characteristics

Age at Diagnostic Biopsy, mean (SD)	20.03 (9.9)
Biopsy Gap*, mean (SD)	4.90 (5.57)
Sex = Male %	51%
Race = White, %	82%
C3GN	26
DDD	6

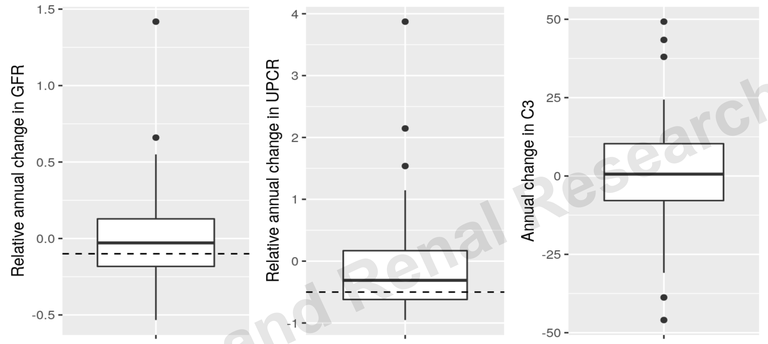


Baseline C3, mg/dl (SD)	84 (51)
Baseline UPCR, mg/mg (SD)	3.3 (4.1)
Baseline eGFR, ml/min/m²	83 (36)

The majority of patients were white, and below the age of 30 at the time of the diagnostic biopsy. M~F. C3 Glomerulonephritis was the most common diagnosis.

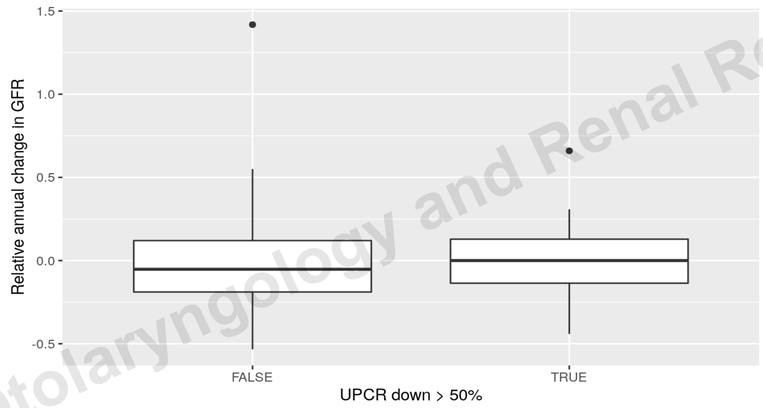
Results

Fig 2. Annual change in clinical parameters



	Mean	Median
GFR slope	-1.7%	-2.9%
UPCR slope	-12.5%	-31.0
C3 slope	1.5mg/dl	0.6mg/dl

Fig 3. Annual change in GFR stratified by UPCR reduction



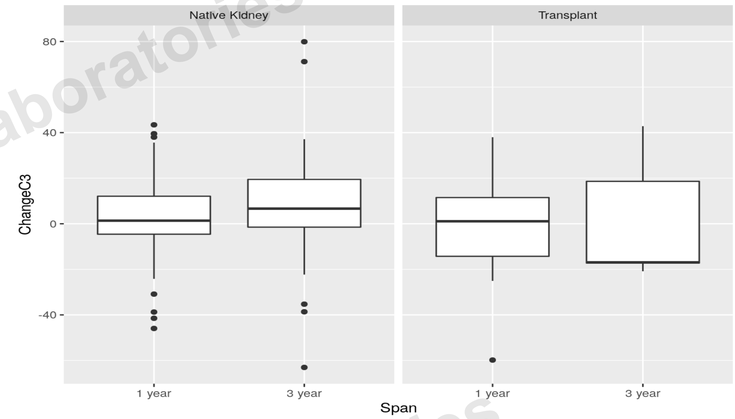
	Mean	Median
GFR slope (UPCR down > 50%), % change/yr	0.2	0.0
GFR slope (otherwise), % change/yr	-2.8	-5.2

P = 0.45

Change in C3:

1. In the 37 spans where a patient had a low C3 at baseline, only 1 (2.7%) achieved a stable GFR and a UPCR reduction of ≥ 50%.
2. The tendency of C3 to change over a one-year period:
   a. In 53.2% of 1-year spans C3 remained within 10 of its baseline level.
   b. In 88.9% of spans C3 remained within 25 of its baseline C3 level.

Fig 4. Variability of C3 over time



	eGFR decrease ≥ 10% No	eGFR decrease ≥ 10% Yes	Percent
Baseline C3 ≥ 90			
UPCR decrease ≤ 50% - No	10	6	37.5%
UPCR decrease ≤ 50% - Yes	6	2	25.0%
Baseline C3 < 90			
UPCR decrease ≤ 50% - No	11	11	50%
UPCR decrease ≤ 50% - Yes	10	5	33.3%

Other than a modest tendency for patients on ACE inhibitors to experience a decline in proteinuria (p = 0.14), no association existed between concomitant medication use and clinical outcomes. (Data not shown)

Conclusions

- An annual change in urine protein (mean decline of 12.5%) was noted under current cares.
- Minimal change in eGFR was noted in a 1 year span.
- C3 appeared to be remarkably stable over a 1-year time span.
- When using a C3 cut off of 90mg/dl (normal), there appear to be no association with baseline C3 level and change in UPCR or GFR over a 1 year time span.
- The two major weaknesses of the current study are the small number of patients and an accounting of the effect of time since biopsy.

Future Directions

- The cohort has now been expanded to 85 patients. Future studies include evaluating the longitudinal history of these same clinical biomarkers from the time of diagnostic kidney biopsy until the time of last follow up (without separation into yearly spans of disease).
- Reassessment will re-stratify based on quartile categories of baseline C3 level.
- Future studies will expand the number of clinical and research biomarkers of disease to be characterized.

References

1. *Kidney Int. 2013 Dec;84(6):1079-89*
2. *Nat Rev Nephrol.* 15(3), 129-143 (2019)
3. *Kidney Int.* 89, 278-288 (2016)
4. *Kidney Int*. 82, 1084–1092 (2012).
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Research is funded in part by the NIH (CMN and RJHS) and an unrestricted grant from Novartis.