Age-Dependent Plasma Factor D Levels and Their Clinical Implications in Complement-Mediated Kidney Diseases

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Background

Atypical hemolytic uremic syndrome (aHUS) and C3 glomerulopathy (C3G) are ultra-rare renal diseases caused by unregulated complement activity of the alternative pathway (AP). C3G subtypes include C3 glomerulonephritis (C3GN) and dense deposit disease (DDD).

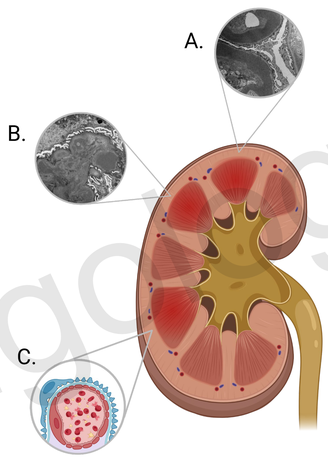

Figure 1. Complement-mediated renal diseases.
A. Dense Deposit Disease (DDD). EM shows sausage-like electron-dense deposits within the glomerular basement membrane.
B. C3 glomerulonephritis (C3GN). EM shows less electron-dense deposits within the glomeruli.
C. aHUS-associated thrombotic microangiopathy resulting in endothelial damage, platelet activation, and schistocytes.

Complement Factor D (FD), also known as adipsin, is a 24 kDa serine protease essential for AP activation and functions as the rate-limiting enzyme. FD is filtered through the glomerular filtration barrier and catabolized in renal tubules. To maintain plasma levels, adipocytes synthesize FD at a high rate; consequently, FD accumulates in patients with renal diseases that cause reduced glomerular filtration rate (GFR). Complement Factor H (FH) regulates C3 convertase activity; however, in end-stage renal disease (ESRD), elevated FD levels may exceed available FH, resulting in additional AP dysregulation.

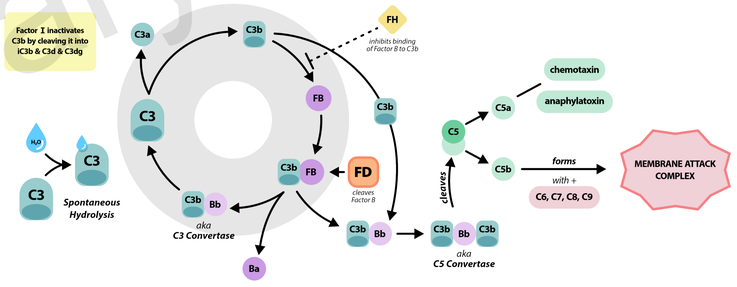

Figure 2. The alternative pathway of the complement system. The AP is initiated through the hydrolysis of C3 to C3(H2O). Factor D (FD) cleaves Factor B (FB) bound to C3(H2O) or C3b to form C3 convertase [C3(H2O)Bb, C3bBb], which cleaves, in turn, more C3 to C3b. Factor H (FH) regulates C3 convertase activity by inhibiting the formation of C3bBb, accelerating the decay of C3bBb, and acting as a cofactor for Factor I-mediated C3b degradation.

C3G most often affects children and young adults, with ~70% of pediatric cases progressing to ESRD within 10 years of diagnosis.[1] In pediatric aHUS, decreased FH activity, commonly due to FH autoantibodies or pathogenic *CFH* variants[2], is the major cause of complement dysregulation. This dysregulation may be amplified (exacerbated) by elevated FD levels in renal disease. Defining normal FD levels in the pediatric population is therefore essential for accurately assessing complement dysregulation in these patients.

Among the complement proteins, FD circulates at the lowest plasma concentration (1–2 mg/L in adults). As FD is primarily synthesized by adipocytes and catabolized through renal tubules, we tested two hypotheses:

1. FD levels in healthy children (lower adipocyte mass) are significantly lower than those in adults, reflecting reduced adipocyte mass and body mass index (BMI).
2. FD levels are elevated in patients with chronic kidney disease (CKD), independent of BMI.

Methods

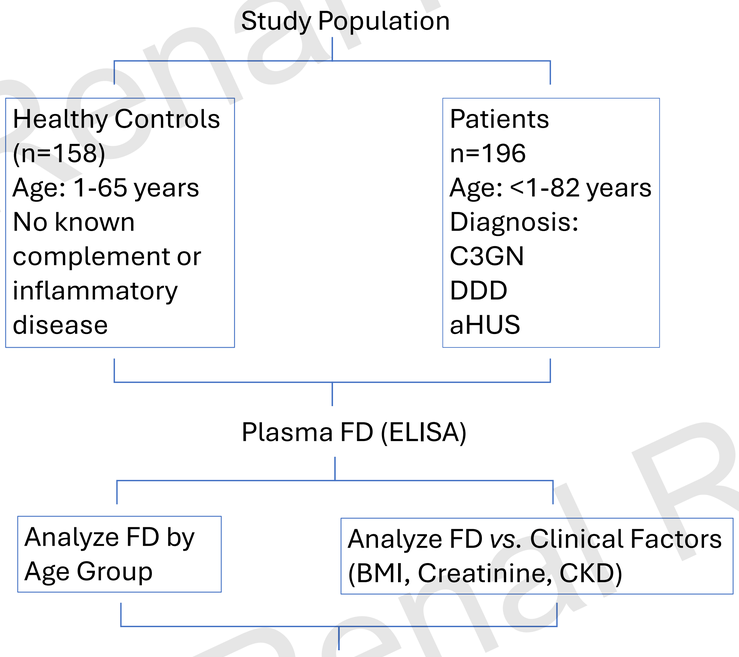

Figure 3. Study design and analysis workflow. The study included 158 healthy controls (ages 1–65 years, no known complement or inflammatory disease) and 196 patients (ages <1–82 years) with diagnoses of C3GN, DDD, or aHUS. Plasma FD levels were measured by ELISA (Hycult) and analyzed by age group and in relation to clinical factors (BMI, creatinine, CKD). Results were used to establish age-specific FD reference ranges and evaluate their diagnostic utility.

Results

In healthy controls, FD levels showed a strong correlation with age (r = 0.83). Among individuals ≥20 years, the mean FD concentration was 1.07 mg/L (median: 1.08 mg/L, ±2 SD: 0.48–1.66 mg/L), whereas in those <20 years, the mean FD level was significantly lower at 0.58 mg/L (median: 0.58 mg/L, ±2 SD: 0.25-0.92 mg/L).

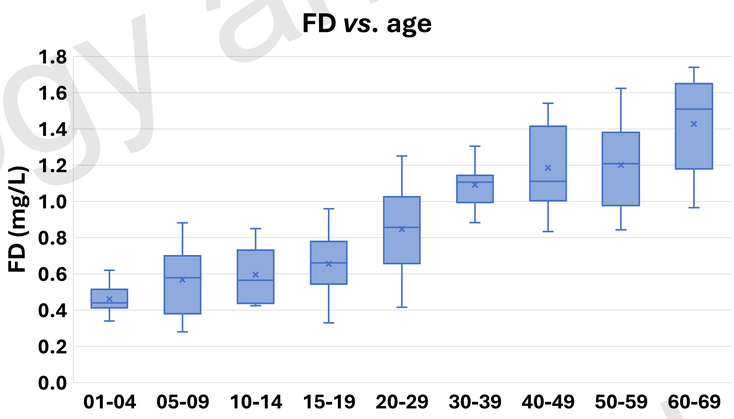

Figure 4. Factor D Levels by Age in Healthy Individuals. Box-and-whisker plots show FD concentrations (mg/L) across age categories. FD levels increased progressively with age, with significantly lower values observed in individuals <20 years compared to adults.

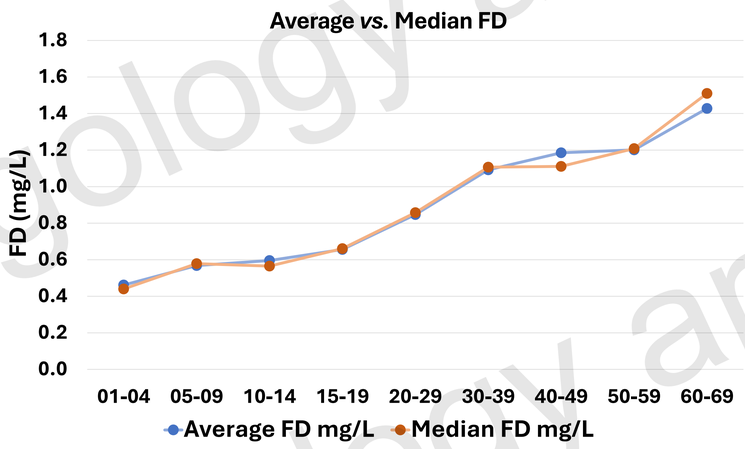

Figure 5. Mean *vs.* Median Factor D levels by Age Group. Comparison, mean vs median FD values by age group in healthy individuals without known complement disease or inflammatory condition. Mean and median FD levels closely align across age groups, indicating a consistent age-related increase in FD without substantial skewing from outliers.

Among patients with complement-mediated kidney disease, FD levels strongly correlated with CKD severity as measured by serum creatinine (r = 0.82) but show no significant correlation with age (r = 0.25) or BMI (r = 0.22).

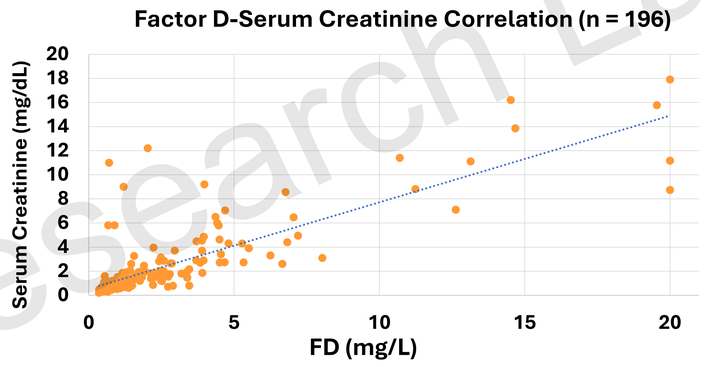

Figure 6. Correlation Between Factor D and Serum Creatinine. A strong correlation (r = 0.82) was observed between plasma FD *vs.* serum creatinine in patients with complement-mediated kidney disease.

Conclusion

This study establishes age-specific FD reference ranges to improve the assessment of complement activity and kidney function in pediatric patients. In addition, we show that FD levels rise with worsening kidney function, independent of BMI. Given its role in AP activation, this increase may contribute to complement dysregulation, further exacerbating kidney injury. Our diagnostic reports classify FD levels as high, normal, and low. Reclassifying pediatric reporting ranges based on age-specific averages and standard deviations could provide physicians with better tools for prognosis and treatment decisions in patients under 20.

Table 1. Normal Factor D ranges by age group

Age Group	Average FD (mg/L)	Min (mg/L)	Max (mg/L)	Median (mg/L)	n
01-19	0.58	0.34	0.96	0.58	65
>20	1.07	0.42	1.74	1.08	93

FD values in pediatric *vs.* adult healthy subjects without known complement or inflammatory disorders.

Table 2. FD Level Cutoff Values for Adult *vs.* Pediatric

Classification	Adult Cutoff (mg/L)	Pediatric Cutoff (mg/L)
Low	< 0.78	< 0.35
Normal	0.78-1.59	0.36-0.92
High	> 1.59	> 0.92

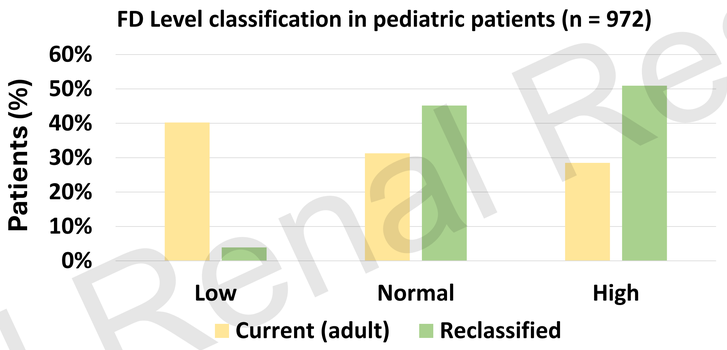

Figure 7. Impact of Pediatric-Specific FD Cutoffs on Classification. Reclassification of FD levels in pediatric patients using pediatric-specific cutoff values leads to a marked decrease in 'Low' classifications and increases in 'Normal' and 'High' classifications.

References:
1. Smith RJH, Appel GB, Blom AM, et al. C3 glomerulopathy - understanding a rare complement-driven renal disease. *Nat Rev Nephrol*. 2019;15(3):129-143. doi:10.1038/s41581-018-0107-2
2. Michael M, Bagga A, Sartain SE, Smith RJH. Haemolytic uraemic syndrome. *Lancet*. 2022;400(10364):1722-1740. doi:10.1016/S0140-6736(22)01202-8

Acknowledgements
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