

## Gender Differences in the Lupus Nephritis Biomarkers in Children

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**Background/Purpose:** Lupus nephritis (LN) is frequently associated with a poor long-term prognosis. The non-invasive traditional measures of LN (LN-TM) currently used to monitor LN have limited responsiveness to change. Though the discovered and initially validated promising LN biomarkers (i.e. the LN-Panel) accurately reflect LN activity & chronicity as seen on kidney biopsy, and can forecast LN flares, however, there remains an important unknown in regards whether the LN-Panel biomarkers are influenced in their levels by patient gender. The objective of this study is to assess the gender and age specific differences in the levels of the LN-Panel biomarkers and to establish normative values of the combinatorial biomarkers in healthy children.

**Methods:** Urine concentrations of the LN biomarkers Neutrophil gelatinase associated lipocalin (NGAL), Monocyte chemoattractant protein-1 (MCP1), Ceruloplasmin (CP), Alpha1-acid glycoprotein (AGP), Transferrin (TF) and Lipocalin-like prostaglandin-D Synthase (LPDGS) were measured by nephelometry or ELISA in select male and female pediatric LN patients. All the biomarkers were logarithmically transformed and standardized to urinary creatinine concentration. Student t test was used to compare means of the LN panel biomarkers between female and male active LN patients. A fixed effect model was used to compare means after adjusting for differences in clinical measures of LN activity using the Renal SLEDAI domain scores. P value of  $<0.05$  was considered statistically significant.

**Results:** In a sample of 64 females and 12 males with childhood LN, the means of urinary MCP-1 was significantly elevated in females compared to males (table 1). Also the means of urinary LPGDS was significantly elevated in 27 female patients who had histological feature of Epimembranous deposits compared to 6 males (table2). There were also significant gender differences in select LN Panel biomarkers when looking at the activity and chronicity of LN on kidney biopsy (see Table 3).

**Conclusion:** This study supports that there are gender differences in select LN-Panel markers. Also these differences can be seen with certain type of underlying histological features of LN.

**Table 1: Gender related differences in LN-Panel with LN adjusted for differences in clinical measures of LN activity using the Renal SLEDAI domain scores**

Type of Biomarker *	Biomarker	Female (n=64)	Male (n=12)	P-value
<b>Select LN-Panel Biomarkers</b>	<b>NGAL</b>	3.50 ± 1.18	2.83 ± 1.68	0.097
	<b>MCP1</b>	<b>0.00 ± 1.10</b>	<b>-0.95 ± 0.89</b>	<b>0.013</b>
	<b>CP</b>	8.91 ± 1.47	8.42 ± 1.24	0.299
	<b>ACG</b>	10.60 ± 1.41	10.34 ± 1.52	0.584
	<b>TF</b>	1.83 ± 1.43	1.36 ± 1.19	0.328
	<b>LPGDS</b>	-0.59 ± 0.90	-1.10 ± 1.23	0.103
<b>Traditional LN Measures</b>	<b>BP(syst)</b>	129.03 ± 21.58	138.17 ± 23.60	0.189
	<b>BP(diast)</b>	80.66 ± 15.03	81.25 ± 15.98	0.901
	<b>Serum BUN</b>	2.84 ± 0.65	2.80 ± 0.83	0.852
	<b>Serum creatinine</b>	-0.06 ± 0.53	0.16 ± 0.67	0.197
	<b>Urine prot/crea ratio</b>	0.83 ± 1.10	0.38 ± 1.34	0.217
	<b>Complement C3</b>	4.15 ± 0.50	4.14 ± 0.46	0.956
	<b>Complement C4</b>	2.43 ± 0.72	2.54 ± 0.57	0.642

\*Values are mean ± SD of LOG transformed in serum & urine biomarkers; the LN-Panel markers are all standardized by urine creatinine

**Table 2: Some LN Panel biomarkers differ with histological features by gender**

Biomarker	Epimembranous deposits					
	Absent			Present		
	Female (N=37)	Male (N=6)	p-value	Female (N=27)	Male (N=6)	p-value
NGAL	3.51 ± 1.25	3.19 ± 1.81	0.574	3.48 ± 1.10	2.46 ± 1.62	0.081
MCP-1	0.02 ± 1.11	-0.97 ± 0.81	0.093	-0.03 ± 1.12	-0.94 ± 1.02	0.077
CP	8.70 ± 1.66	8.33 ± 1.63	0.600	9.20 ± 1.13	8.49 ± 0.96	0.275
ACG	10.43 ± 1.32	10.17 ± 1.67	0.703	10.82 ± 1.52	10.49 ± 1.53	0.606
TF	1.59 ± 1.51	1.40 ± 0.85	0.801	2.15 ± 1.27	1.33 ± 1.46	0.201
LPGDS	-0.74 ± 0.98	-0.87 ± 1.22	0.777	<b>-0.37 ± 0.74</b>	<b>-1.29 ± 1.32</b>	<b>0.035</b>

**Table 3: Some LN Panel biomarkers show gender differences with the activity and chronicity of LN on kidney biopsy.**

LN-Panel	Active kidney inflammation: Biopsy NIH-Activity Score (range 0 -24)						Kidney damage: Biopsy NIH-Chronicity Score (0-12)					
	NIH-AI score <7			NIH-AI score ≥7			NIH-CI <4			≥4 (or w. Chronicity)		
	Female (N=53)	Male (N=11)	p	Female (N=11)	Male (N=1)	p	Female (N=55)	Male (N=10)	p	Female (N=9)	Male (N=2)	p
NGAL	3.41 ± 1.22	2.89 ± 1.75	0.22	3.92 ± 0.90	2.11 ± 0.00	0.17	<b>3.49 ± 1.09</b>	<b>2.61 ± 1.72</b>	<b>0.04</b>	3.55 ± 1.73	3.89 ± 1.32	0.73
MCP-1	<b>-0.20 ± 1.05</b>	<b>-0.95 ± 0.89</b>	<b>0.03</b>	0.89 ± 0.84	N/A	N/A	<b>-0.08 ± 1.02</b>	<b>-1.17 ± 0.84</b>	<b>0.01</b>	0.34 ± 1.41	-0.07 ± 0.46	0.62
CP	8.66 ± 1.43	8.43 ± 1.31	0.61	10.09 ± 1.05	8.32 ± 0.00	0.22	8.97 ± 1.35	8.30 ± 1.34	0.20	8.53 ± 2.13	8.95 ± 0.56	0.71
ACG	10.39 ± 1.40	10.27 ± 1.59	0.81	11.60 ± 0.99	11.01 ± 0.00	0.69	10.60 ± 1.44	10.20 ± 1.41	0.44	10.57 ± 1.29	10.98 ± 2.52	0.72
TF	1.57 ± 1.38	1.43 ± 1.25	0.75	2.96 ± 1.10	0.74 ± 0.00	0.11	1.81 ± 1.38	1.24 ± 1.23	0.29	1.96 ± 1.81	1.83 ± 1.27	0.90
LPGDS	-0.64 ± 0.91	-1.10 ± 1.29	0.16	-0.31 ± 0.83	-1.07 ± 0.00	0.45	<b>-0.59 ± 0.88</b>	<b>-1.29 ± 1.29</b>	<b>0.04</b>	-0.53 ± 1.05	-0.24 ± 0.13	0.69