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Association of Uremic Toxins with Immunosenescence in Patients with Chronic Kidney Disease

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Objectives : Cardiovascular diseases and infections, which are common manifestations of immunosenescence, are two major causes of mortality in patients with CKD. Uremic toxins have been shown to induce immune dysfunctions in basic studies. However, little is known about the association of uremic toxins with immunosenescence among patients with CKD.
Methods : We investigated the association of four gut-derived uremic toxins, including indoxyl sulfate (IS), p-cresyl sulfate (pCS), trimethylamine-N-oxide (TMAO), and phenylacetylglutamine (PAG), with the presence of immunosenescence in a cross-sectional cohort of patients with CKD. Immunosenescence was defined as percentage of CD57+ in terminal effector (TE) CD8+ T cells >50%. Plasma uremic toxins were quantified by high performance liquid chromatography. Nutritional status was assessed by using the Controlling Nutritional Status (CONUT) score. We further performed an in vivo study to support the association.
Results : A total of 131 patients with non-dialysis stages 3–5 CKD were included. In multivariate logistic regression model adjusted for age, sex, current smoking history, diabetes, CVD, and the CONUT score, we found that immunosenescence was significantly associated with plasma IS (odds ratio 1.65, 95% confidence interval 1.08 to 2.50) and PAG (odds ratio 1.46, 95% confidence interval 1.03 to 2.06). The results were consistent when percentage of CD57+ in TE CD8+ T cells were treated as a continuous variable. In cultured human PBMCs, IS stimulated expression of inflammatory markers (tumor necrosis factor-α and interferon-γ) as well as immunosenescence biomarkers (PD-1 and CD57) on CD4+ and CD8+ T cells.
Conclusions : Our findings suggest that uremic toxins may be involved in the pathogenesis of immunosenescence in patients with CKD.

Table 1.jpg

Table 1. Characteristics of the study population according to CKD severity

Variable	Moderate CKD[1] (*n*=34)	Severe CKD[2] (*n*=97)	*P* value
Age (years)	61.4 ± 13.1	64.9 ± 11.9	0.153
Male sex, *n* (%)	23 (67.6%)	50 (51.5%)	0.104
Current smoker, *n* (%)	2 (5.9%)	11 (11.3%)	0.360
Diabetes mellitus, *n* (%)	14 (41.2%)	41 (42.3%)	0.912
CVD, *n* (%)	7 (20.6%)	23 (23.7%)	0.709
Hypertension, *n* (%)	26 (76.5%)	83 (85.6%)	0.222
Systolic BP (mmHg)	126.6 ± 18.2	141.1 ± 21.4	0.001
Body mass index (kg/m^2)	26.0 ± 4.7	26.2 ± 4.2	0.818
eGFR (ml/min/1.73 m^2)	39.4 (33.0–46.5)	16.3 (11.5–23.0)	<0.001
Proteinuria (g/day)	0.45 (0.24–1.02)	1.09 (0.55–1.95)	0.001
Albumin (g/dL)	4.4 ± 0.4	4.1 ± 0.4	0.001
Plasma glucose (mg/dL)	110 (98–125)	106 (97–125)	0.767
Total cholesterol (mg/dL)	153 (139–180)	158 (131–190)	0.741
Triglycerides (mg/dL)	117 (88–148)	132 (86–182)	0.420
LDL-C (mg/dL)	82 (76–112)	86 (64–110)	0.469
Phosphorus (mg/dL)	3.5 (3.2–3.8)	4.4 (3.8–5.1)	<0.001
Intact-PTH (pg/mL)	70 (50–99)	187 (110–379)	<0.001
CRP (mg/dL)	0.10 (0.03–0.21)	0.10 (0.03–0.30)	0.740
Interleukin-6 (pg/mL)	2.20 (0.75–3.88)	3.30 (1.90–5.10)	0.027
Indoxyl sulfate (mg/L)	1.31 (0.94–2.22)	3.56 (1.66–7.60)	<0.001
p-cresyl sulfate (mg/L)	3.61 (1.35–7.35)	8.17 (3.66–18.09)	<0.001
TMAO (μM)	7.70 (5.19–13.88)	18.37 (13.30–31.46)	<0.001
Phenylacetylglutamine (μM)	3.85 (1.83–7.83)	14.61 (6.08–30.56)	<0.001

BP, blood pressure; CRP, C-reactive protein; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; PTH, parathyroid hormone; TMAO, trimethylamine-N-oxide.

[1]eGFR ≥30 ml/min per 1.73 m^2

Table 1.jpg

Table 2. Association of uremic toxins with immunosenescence

Variables	Univariate		Multivariate[1]	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Ln (Indoxyl sulfate), mg/L	1.46 (1.01, 2.13)	0.047	1.65 (1.08, 2.50)	0.020
Ln (*p*-cresyl sulfate), mg/L	1.09 (0.82, 1.44)	0.567	1.17 (0.86, 1.59)	0.317
Ln (TMAO), μM	1.37 (0.82, 2.27)	0.230	1.42 (0.80, 2.51)	0.228
Ln (Phenylacetylglutamine), μM	1.29 (0.95, 1.75)	0.110	1.46 (1.03, 2.06)	0.033

CI, confidence interval; OR, odds ratio; TMAO, trimethylamine-N-oxide.

[1]Adjust for age, sex, current smoking history, diabetes, CVD, and Controlling Nutritional Status (CONUT) score.