A possible role of P-cresyl sulfate and indoxyl sulfate as biomarkers in the prediction of renal function and CKD progression

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BACKGROUND AND AIM

Protein-Bound Uremic Retention Solutes (PBURS) accumulate in chronic kidney disease (CKD) patients. Among protein-bound compounds, indoxyl sulfate (IXS) and p-cresyl sulfate (PCS) derived from gut bacterial transformation, play an important role. Recent evidences demonstrate their toxic effects in vitro and may contribute in vivo to CKD progression and mortality in uremic patients. For this reason, bacterial metabolism and its metabolites are therapeutic targets in CKD. The association between PBURS and CKD-associated immune dysfunction has recently emerged. In this study, PCS and IXS are considered to highlight the possible role as biomarkers in the prediction of renal function according to the stage of progression (CKD stage: GFR stage 1-5).

METHODS

In our observational, prospective study we evaluated total (t) and free (f) PCS and IXS plasmatic fractions (B.S.N srl) using Ultra High Performance Liquid Chromatography Infinity 1260 (Agilent technologies) coupled to an API 3200™ triple quadrupole mass spectrometry (ABSciex). Urea and Creatinina measured by Dimension Vista® (SIEMENS Healthcare)

Renal function was determined by eGFR (formula CKD-EPI, K/DOQI guidelines) and CKD stage defined by GFR (G) stages (1-5) by eGFR (formula CKD-EPI) (K/DOQI guidelines)

Data were shown as mean ± SD or median (25th-75th). Statistical analysis was done by SPSS version 24.0

RESULTS

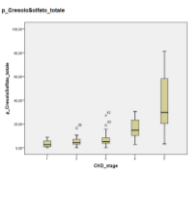
We evaluated 80 CKD patients: 54.68 ± 12.88 yrs, 39 F and 41 M. The median creatinine was 1.58 (0.90-3.32) mg/dL, median urea 58.50 (42.0-121.25) mg/dL and eGFR (CKD-EPI) 42 (17.25-85.75) mL/min/1.73 m2. On the table 1, it was summarized the levels of PCS and IXS in all patients and classified by GFR (G) stages.

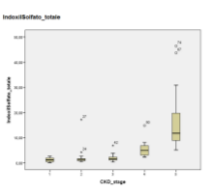
We found the statistically significant increase of total and free fractions of PCS ($p<0.001$) and IXS ($p<0.001$) with the progression of CKD by G stage and inverse strong correlation between eGFR (CKD-EPI) and PCSt (Spearman's Rho (r)=-0.70, $p<0.001$), PCSf (r=-0.75, $p<0.001$), IXSt (r=-0.76, $p<0.001$), IXSf (r=-0.82, $p<0.001$).

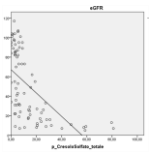
Moreover, the increase of PCS and IXS predicts the eGFR decline significantly, according to the linear regression model using eGFR as dependent variable: PCSt (R-squared (R2)= 0.34, $p<0.001$). PCSf (R2=0.21, $p<0.001$). IXSt (R2=0.27, $p<0.001$). IXSf (R2=0.19, $p<0.001$). By multivariate analysis, the total compounds of both toxins remain predictive of eGFR: PCSt (β=-0.72, p=0.003; 95%CI:-2.43;-0.54) and IXSt (β=-0.70, p=0.011; 95%CI:-5.15;-0.70).

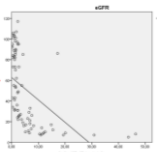
Table 1

	PCSt (mg/L)	PCSf (mg/L)	IXSt (mg/L)	IXSf (mg/L)
ALL pts	6.42 (3.15–19.81)	0.02 (0.00–0.33)	2.27 (1.17 – 6.78)	0.04 (0.01–0.15)
G1 (20pts)	2.7 (0.78–5.94)	0.00 (0.00–0.00)	1.15 (0.41–1.99)	0.01 (0.00–0.01)
G2 (20pts)	4.26 (2.94–7.84)	0.00 (0.00–0.00)	1.33 (0.85– 1.73)	0.01 (0.00–0.00)
G3 (20pts)	4.86 (3.17–9.41)	0.01 (0.0–0.14)	1.46 (1.07 – 2.29)	0.04 (0.01–0.05)
G4 (20pts)	14.74(8.82–23.72)	0.22 (0.06–0.36)	4.92 (2.98–6.84)	0.09 (0.06–0.15)
G5 (20pts)	29.74 (20.23–58.34)	0.73 (0.29–1.34)	11.76 (8.12–19.91)	0.38 (0.23–0.53)









CONCLUSION

In conclusion, in our study we showed the strong correlations between PCS and eGFR; IXS and eGFR. PCS and IXS (total and free) increased significantly along with the progression of CKD in all G stage (1-5). We highlighted the use of mass spectrometry in the evaluation of renal function especially in the earliest stages of CKD with the possibility of measuring minimum concentrations of PCSf and IXSf.

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