Exploring protein binding of uraemic toxins in patients with different stages of chronic kidney disease and during haemodialysis

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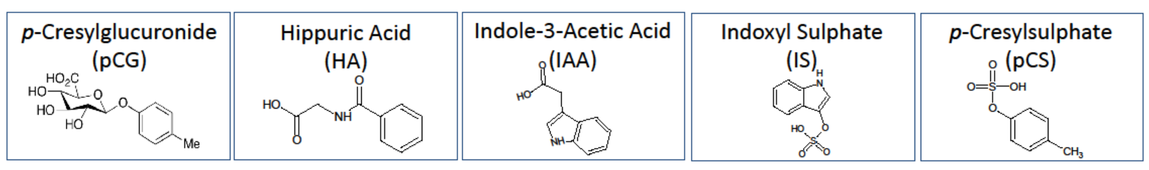
INTRODUCTION

The **uraemic syndrome** is characterised by the retention of so-called uraemic toxins, which are classified into three groups: free small water soluble solutes (MW<500Da), middle molecules (MW>500Da) and **protein-bound solutes** [1,2].

It can be hypothesised that the degree of **protein binding changes** in individual patients with the **progression of their CKD**. Also, degree of protein binding can potentially be influenced by **haemodialysis** treatment.

In this study, we evaluated the **percentage protein binding (%PB)** in different stages of CKD (i.e. stage 2 to 5) as well as during a haemodialysis session in dialysis patients.

PATIENTS AND METHODS



CKD Patients

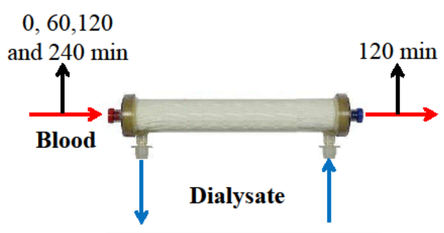
95 CKD patients (stage 2-5)
Amiens University Hospital [3-5]

Sampling: In the morning on the occasion of a visit at outpatient clinic

HD Patients

10 stable HD patients
Ghent University Hospital

Sampling: At midweek session



	CKD 2-5	CKD 2	CKD 3	CKD 4	CKD 5
Number, n (%)	95 (100)	11 (11.5)	37 (39)	37 (39)	10 (10.5)
Age (years)	69[59;76]	62[59;71]	74[61;77]	69[55;74]	79[60;83]
Male gender, n (%)	59 (62)	9 (82)	24 (65)	22 (60)	4 (40)
BMI (kg/m²)	29[25;32]	27[21;29]	29[25;32]	29[26;34]	25[23;30]
DM, n (%)	45 (47)	4 (36)	19 (51)	18 (49)	4 (40)
[Albumin] (g/L)	39[35;44]	42[37;47]	38[35;42]	41[35;44]	33[28;39]
Renal Function (mL/min)	32[20;49]	67[63;71]	45[35;51]	22[19;25]°,+	11[9;13]°,+

°P<0.05 *versus* CKD 2
+P<0.05 *versus* CKD 3

	HD Patients
Number	10
Age (years)	72[61;78]
Male gender, n (%)	8 (80)
BMI (kg/m²)	28[25;28]
DM, n (%)	5 (50)
[Total Protein] (g/L)	60[58;67]
Renal Function (mL/min)	2.6[0.0;4.1]

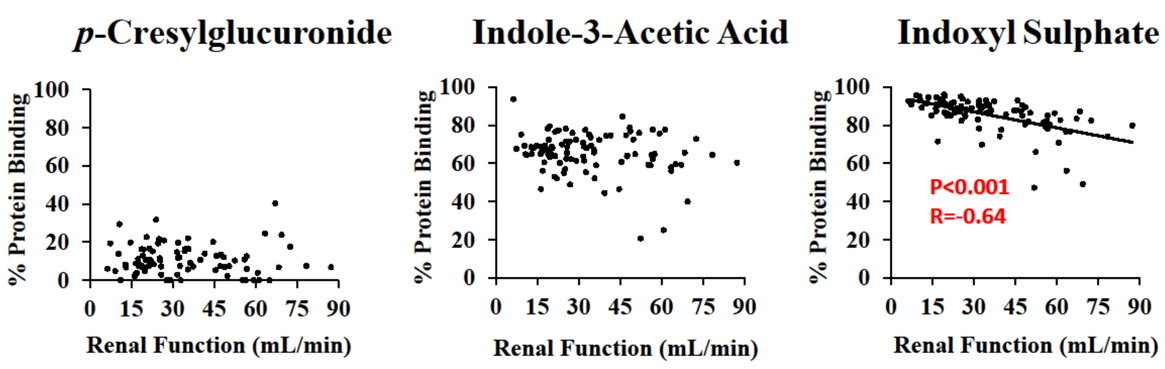
$$\%PB = \left(1 - \frac{[Free]}{[Total]}\right) \times 100\%$$

RESULTS

CKD Patients

	CKD 2-5	CKD 2	CKD 3	CKD 4	CKD 5
pCG	9[6;15]	7[3;24]	10[6;14]	9[6;16]	8[5;20]
HA	38[34;44]	38[34;42]	38[34;43]	38[35;44]	43[36;45]
IAA	66[61;72]	60[56;66]	67[61;75]	66[61;72]	68[65;71]
IS	88[83;91]	77[71;83]	86[80;90]	89[87;92]°,+	92[90;95]°,+
pCS	96[94;97]	93[89;96]	97[96;97]°	96[95;97]	94[93;95]+

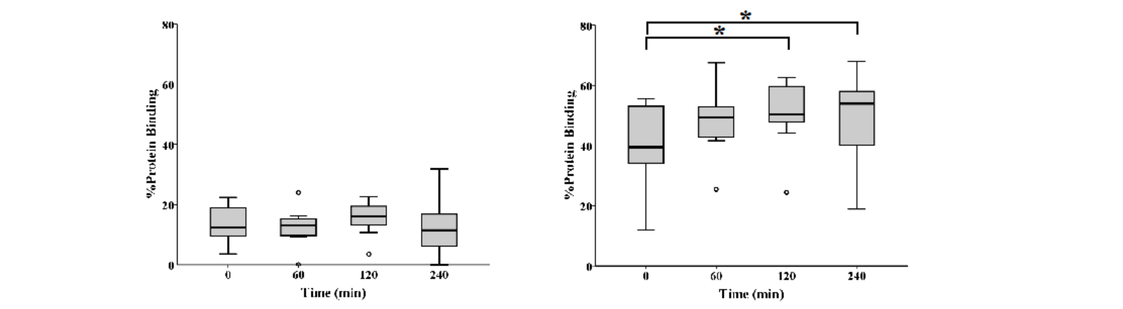
°P<0.05 *versus* CKD 2
+P<0.05 *versus* CKD 3



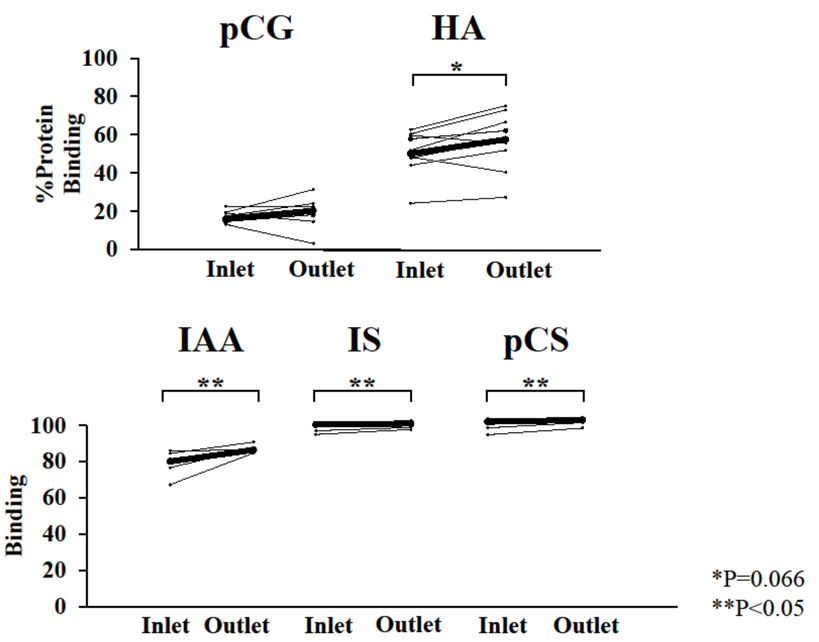
Only %PB of IS showed an inverse correlation with renal function.

HD Patients

%PB during course of HD session



%PB at inlet and outlet of the dialyser



DISCUSSION & CONCLUSION

%PB of the highly bound IS increased with advanced CKD stages

- **No correlation** between %PB and [albumin].
- Is result a consequence of **structural changes** (due to an increase in post-translational modifications of the proteins in advanced CKD stages [6]?
- Is result a consequence of **competitive binding**?

%PB increased during the dialysis session and at the outlet of the dialyser with respect to the inlet, most pronounced for IAA, IS and pCS

- **No correlation** between Δ%PB and Δ[Total Protein].
- A **possible explanation: protein binding** of IAA, IS and pCS is **strong**.

→ Equilibrium is too slow to restore the blood concentration of the free toxin within the time frame of a single passage through the dialyser and within the time frame of a dialysis session once pre-dialysis free fraction has been removed.

Percentage protein binding of IS was higher in more advanced **CKD**.
%PB was increased during the **HD** session, most pronounced for the stronger (IAA) and highly (IS and pCS) bound solutes. These findings might imply a slow release of bound solute from the ligand-protein, resulting in fast exhaustion of free (dialysable) solutes, leading to hampered removal.

[1] Duranton F *et al.*, *J Am Soc Nephr,* 2012; [2] Vanholder R *et al.*, *Kidney Int,* 2003; [3] Barreto FC *et al.*, *Clin J Am Soc Nephrol*, 2009; [4] Liabeuf S *et al.*, *Nephrol Dial Transpl,* 2010; [5] Liabeuf S *et al.*, *Plos One,* 2013; [6] Gajjala PR *et al.*, *Nephrol Dial Transpl* 2015 (In press).

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