Reduced protein bound uraemic toxins in vegetarian kidney failure patients treated by haemodiafiltration

Sakina Kandouz¹, Ali Shendi Mohamed Ali²,³, Yishan Zheng⁴, Susan Sandeman⁴, Andrew Davenport¹

¹UCL Centre for Nephrology, Royal Free Hospital, University College London Medical School, London, UK
²ISN / UKRA fellow, UCL Centre for Nephrology, Royal Free Hospital, University College London Medical School, London, UK
³Zagazig University, Markaz El-Zakazik, Ash Sharqia Governorate 44516, Egypt
⁴Department of Pharmacy & Biomolecular Sciences, Brighton University, Brighton, UK

Sakina Kandouz s.kandouz@gmail.com
Ali M Shendi Mohamed dr_aly_shindy@yahoo.com
Yishan Zheng yz9@brighton.ac.uk
Susan Sandeman S.Sandeman@brighton.ac.uk
Andrew Davenport andrewdavenport@nhs.net

Address for correspondence andrewdavenport@nhs.net
UCL Centre for Nephrology Royal Free Hospital Pond Street London NW3 2QG
Tel 44-2074726457 Fax 44-2073178591

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Short title vegetarian diet and uraemic toxins

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Abstract

Introduction. Indoxyl sulfate (IS) and p cresyl sulfate (PCS) are protein bound toxins which accumulate with chronic kidney disease. Haemodiafiltration (HDF) increases middle molecule clearances and has been suggested to increase IS and PCS clearance. We therefore wished to establish whether higher convective clearances with HDF would reduce IS and PCS concentrations.

Methods. We measured total plasma IS and PCS in a cohort of 138 CKD5d patients treated by On-line HDF (Ol-HDF), by HPLC.

Findings. Mean patient age was 64.6±16.5 years, 60.1% male, 57.3% diabetic, median dialysis vintage 25.9 months (12.4-62.0). The mean ICS concentration was 79.8±56.4 umol/l and PCS 140.3±101.8 umol/l. On multivariate analysis, IS was associated with serum albumin (β 4.31, p<0.001), and negatively with residual renal function (β -4.1, p=0.02) and vegetarian diet (β -28.3, p=0.048) and PCS negatively with log CRP (β -75.8, p<0.001) and vegetarian diet (β -109, p=0.001). Vegetarian patients had lower IS and PCS levels (median 41.5 (24.2-71.9) vs 78.1 (49.5-107.5) and PCS (41.6 (14.2-178.3) vs 127.3 (77.4-205.6) umol/l respectively, p<0.05. Vegetarian patients had lower preOl-HDF serum urea, and phosphate (13.8 ±3.8 vs 18.4 ±5.2 mmol/l, and 1.33 ±0.21 vs 1.58 ±0.45 mmol/l), and estimated urea nitrogen intake (1.25±0.28 vs 1.62 ±0.5 g/kg/day ) respectively, all p<0.05

Conclusions. Plasma IS and PCS concentrations were not lower with Ol-HDF compared to previous studies in haemodialysis patients. However those eating a
vegetarian diet had reduced IS and PCS concentrations. Although this could be
due to differences in dietary protein intake, a vegetarian diet may also
potentially reduce IS and PCS production by the intestinal microbiome.

Introduction

Chronic kidney disease (CKD) leads to the accumulation of nitrogenous
waste products of metabolism. The mortality of CKD patients treated by dialysis
(CKD5d) remains high, and intuitively a greater amount of dialysis designed to
remove these toxins would be expected to increase patient survival. The National
Co-operative Dialysis Study (NCDS), demonstrated that short term patient
outcomes were determined by the time averaged urea concentration. The results
from the NCDS were used to define a critical threshold for haemodialysis urea
clearance as a sessional Kt/Vurea [12]. However a subsequent randomised
prospective haemodialysis study (HEMO study) [3], did not show that higher
dialyzer urea clearances improved patient survival.

Although urea accumulation can lead to carbamylation of haemoglobin and
other proteins [4,5], urea is only one of a number of potential toxins that
accumulate in CKD5d patients [6]. Serum beta 2 microglobulin, a middle sized
azotaemic toxin, has been linked to an increased cardiovascular mortality and
secondary analysis of the HEMO study also reported an association between
increasing serum beta 2 microglobulin concentrations and mortality [7]. Although
this effect of increasing beta 2 microglobulin may be due to loss of residual renal
function, or inflammatory states, rather than reduced dialyzer beta 2 microglobulin clearance.

As the prospective randomised Membrane Permeability Outcome (MPO) trial was designed to compare high and low flux dialyzers did not observe any overall survival advantage with high flux dialyzers [8]. Although haemodiafiltration, which increases middle sized solute clearances [9], was described more than 50 years ago [10], it is only in recent times that haemodiafiltration has become an established treatment for many patients in Europe. Studies delivering the highest convective clearances reported a survival benefit for on-line haemodiafiltration (Ol-HDF) [11], whereas trials delivering lower convective doses did not [12]. Although these studies differed in patient characteristics including age, dialysis vintage and residual renal function, there was a suggestion that Ol-HDF, by improving the spectrum of azotaemic toxin removal may increase dialysis patient survival [13]. There has been debate as to whether HDF increases clearance of indoxyl sulfate and p-cresyl sulfate, with some studies reporting increased clearance [14].

As such we wished to determine whether there was an effect of convection on the removal of these protein bound azotaemic toxins.

Patients and methods

We measured total plasma indoxyl sulfate and p-cresylsulfate in 138 established chronic kidney dialysis patients attending for routine outpatient Ol-HDF treatments under the care of the Royal Free Hospital, using Fresenius
4008H, 5008 (Fresenius AG, Bad Homburg, Germany) or BBraun Dialogue+ (BBraun, Melsungen, Germany) dialysis machines, with high flux polysulphone dialyzers (Nipro, Osaka, Japan) [15], and anticoagulated with tinzaparin (Leo Laboratories, Market Harborough, UK) [16]. Ultrapure quality water was used for all treatments.

Serum biochemistry samples were analysed with a standard multi-channel biochemical analyzer (Roche Integra, Roche diagnostics, Lewes, UK), using the bromocresol green method for albumin determination, and the same assay for C reactive protein (CRP) as the UK National Amyloid Centre. Haemoglobin (Hb) was measured by the sodium lauryl sulphate-Hb method (XE-2100 Sysmex Corporation, Kobe, Japan) [17]. Serum beta-2-microglobulin was measured by rate nephelometry (www.Dako.com, Image 800 analyser, Beckman Coulter, High Wycombe, UK). Dialysate sodium delivery was checked by flame photometry and ion electrophoresis [18]. Patients were weighed pre and post haemodiafiltration using regularly calibrated scales and extracellular water to total body water measured with multifrequency bioelectrical impedance (Biospace 720, Biospace, Seoul, Korea) [19]. Protein nitrogen accumulation was estimated from pre and post dialysis urea concentrations and body water, and then normalised for body weight (nPNA) [20].

Patients were reviewed by renally qualified dieticians, and dietary histories obtained by patient dietary recall. Residual renal function was measured from timed urine collections obtained between the 1st and 2nd OL-HDF
treatments of the week with corresponding blood tests, and expressed as the
average of urea and creatinine clearance.

Indoxyl sulfate (IS) and p cresyl sulfate (p-CS) were measured by
high pressure liquid chromatography (HPLC). In brief 200 ul plasma samples
were incubated for 5 minutes at room temperature with 20ul of competitive
inhibitor sodium caprylate (0.24 umol/l). 20ul of Internal standard naphthalene
sulphonic acid (0.5 mmol/l) was added. Samples were deproteinised by addition
of 2 ml ice cold acetone, centrifugation at 4000 rpm for 10 minutes followed by
the addition of 2 ml ice cold dichloromethane to the resulting supernatant and
further centrifugation at 4000 rpm for 10 minutes. The top aqueous phase was
removed, stabilised with 20ul of 1M HCl and placed in a Waters 717 plus auto-
sampler (Waters Corporation, Milford, Massachusetts, USA) set at 15°C, 10 µl
sample injection, 20 minutes run time, 10 minutes delay. Samples were injected
onto a Fortis C18 column (150 x 4.6 OD, 3 mM) (Fortis Technologies Ltd, Neston,
Cheshire, UK) for peak separation using a Perkin Elmer Series 200 quaternary
gradient pump (Perkin Elmer Life and Analytical Sciences, Shelton, Connecticut,
USA) to control a mobile phase of A (0.2% trifluoroacetic acid in water) and
B(0.2% trifluoroacetic acid in acetonitrile) with a gradient flow of %A/B 85/15
for 5 minutes, 80/20 for 5 minutes, 0/100 for 2 minutes at 0.6 ml/minute flow
rate, 0/100 for 3 minutes at 0.8 ml/min flow rate and 86/15 for 2 minutes at 1
ml/minute flow rate. A Waters 2475 multi wavelength fluorescence detector
was used to detect IS and internal standard at 280/360 nm and p-CS at
260/296 nm excitation/emission wavelength. TotalChrom Navigator-900
software (Perkin Elmer Life and Analytical Sciences, Shelton, Connecticut, USA) was used to collate the peak data via a PE Nelson 900 Series interface [21].

Statistical analysis

All categorical data were reported as number (percentage) and numeric data as mean ± standard deviation (SD). Comparison between two groups was performed with t test or Mann-Whitney U test for non-normally and non-parametric distributed variables, or Chi square test with Yates’ correction. Nonparametric variables were log transformed for correlation analysis. Simple correlation was performed, and variables with p<0.1 were then included in a step backward multiple linear regression analysis to determine which variables were associated with indoxyl sulfate and p-cresyl sulfate concentrations. Variables which were not statistically significant were excluded from analysis unless they improved model fit. Data were analysis by SPSS statistic software (version 22, Chicago, USA). The level of significance was defined as a p value <0.05.

Study approval was granted by the UK NHS national ethics committee IRAS project number 129559, and the study was undertaken in keeping the Helsinki accord with informed patient consent and trial registration ISRCTN70556765.

Results

Total plasma IS and P-CS concentrations were measured in 138 adult patients receiving Ol-HDF, mean age 64.6±16.5 years, 60.1% male, 57.3%
diabetic, median dialysis (Ol-HDF) vintage 25.9 months (12.4-62.0). Stoke-
Davies co-morbidity score 1.0 (1-1) and grade 1 (0-1) [22]. 51 patients were
Caucasoid, 42 South Asian, 37 African-Afro-Caribbean with the remainder being
Asian and one from North Africa. On dietary recall renally trained dieticians
recorded that 16 patients were strict vegetarians and the remainder of the
cohort were omnivores.

Pretreatment haemoglobin was 110.1±17.4 g/l, serum albumin 39.3±4.2 g/l,
urea 17.9±5.3 mmol/l, creatinine 677±254 umol/l, calcium 2.32± 0.13 mmol/l,
phosphate 1.55±0.43mmol/l, glucose7.5±2.7 mmol/l, CRP 6mg/l (2.0-12.3, β2
microglobulin 28.9±10.6mg/l and median 24 hour urine volume 367ml (210-865).
Median dialysis session time 3.75 hours (3.5-4.0), dialyzer surface area 2.1 m²
(1.7-2.1), blood flow 300 ml/min (300-350), litres of convection 15.4 ±2.4 l,
tinzaparin dose 2500 IU (1500-3500), dialysate sodium 136mmol/l (136-137).
Sessional urea reduction ratio was 73.4±7.4%, and single pool Kt/Vurea 1.55±0.32,
with a nPNA 1.58±0.48g/kg/day. Pre-dialysis weight 74.3± 17.3 kg, and 72.4±17.0
kg post dialysis. Extracellular water/total body water ratio pre-dialysis was
0.403±0.013 and post dialysis 0.395±0.021. 55 patients had some residual renal
function, median creatinine clearance 0 (0-2.2) ml/min/1.73m².

54.4% of patients were prescribed antihypertensive medications, median
number of classes of anti-hypertensive medications prescribed per patient 1 (0-
1). 43.9% were prescribed calcium containing phosphate binders, 25.2%
sevelamer hydrochloride 25.2% and 4.3% lanthanum carbonate.
Simple univariate analysis was performed for both plasma IS and PCS (Table 1), and IS was most strongly associated with serum albumin and creatinine and negatively with residual renal function, whereas PCS the associations were weaker but positive for serum urea, and prescription of HMG CoA 3 reductase inhibitors (statins), and co-morbidity. There was no association with convection volumes delivered by Ol-HDF and PCS concentrations, and only a weak correlation between convection volume and IS ($r^2=0.04, p=0.049$). However both IS and PCS were negatively associated with a vegetarian diet. We then performed a backward linear regression analysis (table 2), and IS was independently associated with serum albumin, and negatively with residual renal function and vegetarian diet. Whereas, PCS was associated with statin prescription and negatively with CRP and vegetarian diet.

We then compared those eating a vegetarian diet to those consuming meat (table 3). Vegetarians had lower pre-dialysis serum urea and creatinine concentrations, and dietary nitrogen intake, but did not differ in residual renal function, or dialysis urea based clearances or convective volume exchange achieved. Both IS and PCS were lower in the vegetarian cohort (Figure 1). Serum phosphate was also lower (table 3), despite more patients taking phosphate binders in the meat eaters (77.9% vs 43.8%, Chi square 8.97, $p=0.03$), with no difference in calcium containing phosphate binders prescribed compared to sevelamer or lanthanum (45.9 vs 31.3; 27.0 vs 12.5; and 4.9 vs 0%, respectively).

Although there were no differences in sex, age or diabetes, more vegetarians were South Asians (meat eaters 40.9% Caucasian, 21.3% South Asians and
30.3% African-Afro-Caribbeans, and vegetarians 6.3% Caucasoids; 93.7% South Asians, and 0% African-Afro-Caribbeans respectively, Chi square 35.6, p<0.001).

Correcting muscle mass and body fat for height, to derive muscle and fat indices, then the vegetarian cohort had lower muscle mass, but fat mass was similar (p=0.052) (Figure 2).

Discussion

Indoxyl sulfate and P cresyl sulfate are protein bound toxins which accumulate in patients with chronic kidney disease treated by dialysis. Plasma total concentrations in our cohort are similar to those reported from previous studies in dialysis patients [23]. Although earlier reports suggested that convective dialysis therapies could lead to a reduction in IS and PCS [24], we only observed a weak association between the Ol-HDF convective dose and IS concentrations, and other reports showed no difference in IS or PCS concentrations and different convective therapies [25]. Comparing our cross-sectional cohort data with previous studies, then treatment with Ol-HDF does not appear to lead to a substantial reduction in protein bound solutes. We only found a modest association and dialysis session duration, in keeping with previous reports of marginal differences in IS and PCS plasma concentrations and dialysis session time. Increasing dialyzer surface area has previously been suggested to increase clearance [26], we only found a weak univariate association between plasma IS and PCS and dialyzer surface area, that was lost on multiple linear regression. As we had standardised dialysate flow rates we did
not examine the effect of different dialysate flow rates [26], but there was no
effect of convection volume and PCS concentrations and only a very modest
univariate association with IS concentrations.

There was no association between dialytic urea clearance or convective volume
exchange and PCS concentrations, but there were weak univariate associations
for IS, which were lost on multivariate analysis. In keeping with previous
observations IS concentrations were lower in those dialysis patients who had
retained residual renal function [27].

IS and indoxyl glucuronide are produced from tryptophan derived indoles
following intestinal bacterial metabolism, whereas p-cresyl sulfate and p-cresyl
-glucuronide are derived from p-cresol following bacterial metabolism of
tyrosine. Both are then predominantly bound by albumin. Generally on univariate
analysis we found an association between those variables associated with
increased protein intake, protein turnover, whereas there was a negative
association with residual renal function and those variables associated with
reduced dietary intake. On multivariate analysis, IS was associated with albumin,
which is generally a marker of health and nutritional status, and negatively with
residual renal function and vegetarian diet. Similarly PCS was associated with
statin prescription, a potential surrogate for cardiovascular disease, and also
dietary intake, and these protein bound toxins have been linked to increased
cardiovascular risk for dialysis patients [28]. We suspect that the negative
association with CRP could be secondary to the negative effects of low grade
inflammation on dietary intake. Although it is recognised that acute illnesses can
affect the gastrointestinal biome, and so by altering bacterial numbers and populations could also have an effect in reducing production of these gut derived uraemic toxins [29].

In our dialysis cohort we had a group of predominantly South Asian vegetarians, who had lower plasma IS and PCS levels than their meat eating counterparts. Residual renal function and dialysis treatments were not different. However these vegetarian patients did have a lower estimated dietary protein intake, and lower predialysis serum urea and creatinine concentrations, and lower muscle mass, but similar fat mass. Our study is the first to report that a vegetarian diet leads to lower IS and PCS levels in kidney dialysis patients. Our results are supported by previous studies which have reported that low protein diets reduce serum concentrations of protein bound azotaemic toxins [30], and a small study which reported that the production rate of IS and PCS were lower in healthy vegetarians compared to healthy omnivores [31]. In addition, serum phosphate concentrations were also lower, despite fewer patients prescribed phosphate binders, and studies in vegetarian chronic kidney disease patients have also reported lower phosphate levels thought to be due to differences in plant phytate intake [32].

The bacterial population in the colon changes in patients with chronic kidney failure [29], with a switch to more bacteria capable of producing IS and PCS. It is equally recognised that not only sudden changes in health, but abrupt changes in dietary intake can also lead to changes in the gastrointestinal microbiome [29]. There are differences between animal and vegetable proteins,
and as such, the lower IS and PCS concentrations we report in our vegetarian patients could potentially lead to differences in gut bacterial populations and reduced IS and PCS production. Other studies have shown that a deliberate intervention to increase in dietary fibre for 6 weeks can also reduce IS and PCS concentrations [33] We do not think that this would have a major effect in our dialysis population due to the dietary advice given to restrict higher phosphate containing foodstuffs, such as bran and other high fibre foodstuffs. The majority of our vegetarian patients came from the South Asian community, and this group of patients have better 5 year survival on dialysis than Northern Europeans. Although our study is cross sectional, we report for the first time that vegetarian dialysis patients have lower IS and PCS levels, and as such further prospective interventional studies are required to investigate whether changes in diet can reduce protein bound and other uraemic toxins [34].

The authors have no conflicts of interest
The data contained in this paper have not been previously published
Authorship
Sakina Kandouz, Ali Shendi Mohamed Ali, Yishan Zheng and Susan Sandeman collected, processed and analysed samples. Andrew Davenport organized ethical approvals. All authors contributed to drafting the paper and approved the final version.

References


Figure 1. Plasma concentrations of indoxyl sulfate and p cresyl sulfate in non-vegetarian and vegetarian patients. Results expressed as median (interquartile range).* p<0.05 vs non-vegetarian

Figure 2. Muscle and Fat mass measured post haemodiafiltration by multifrequency bioimpedance indexed to height. Results expressed as median (interquartile range) * p<0.05 vs non-vegetarian.
Table 1. Pearson correlation analysis for indoxylsulfate (IS) and p-cresyl sulfate (PCS). Nonparametric data were transformed prior to analysis. Serum variables pre midweek dialysis session. Residual renal function (RRF - combined 24 hour urinary urea and creatinine clearance), dialyzer surface area (dialyzer) Number of classes of antihypertensive medications (No BPmeds), sessional Kt/V (Kt/V), dialysate potassium (Potassium D, sodium (Dialysate Na), β2 microglobulin (β2M), phosphate binders (binders), total body water (TBW), litres of convective clearance (litres), prescription HMG CoA 3 reductase inhibitor (statin). Stoke-Davies Co-morbidity grade (comorbidity), dialysis session time (time), C reactive protein (CRP), g urea nitrogen/kg/day, G N/day/kg

<table>
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<tr>
<th></th>
<th>IS</th>
<th>p</th>
<th>PCS</th>
<th>r</th>
<th>p</th>
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<td>PCS</td>
<td>0.362</td>
<td>&lt;0.001</td>
<td>IS</td>
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<tr>
<td>albumin</td>
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<td>&lt;0.001</td>
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<td>creatinine</td>
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<td>urea</td>
<td>0.206</td>
<td>0.015</td>
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<td>No BP meds</td>
<td>0.225</td>
<td>0.008</td>
<td>CRP</td>
<td>-0.18</td>
<td>0.035</td>
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<tr>
<td>Kt/V</td>
<td>-0.204</td>
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<td>G N/day/kg</td>
<td>0.172</td>
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<td>Potassium D</td>
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<td>0.024</td>
<td>time</td>
<td>0.170</td>
<td>0.046</td>
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<td>vegetarian</td>
<td>-0.192</td>
<td>0.024</td>
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<tr>
<td>Sodium D</td>
<td>-0.182</td>
<td>0.033</td>
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<td>β2 M</td>
<td>0.184</td>
<td>0.031</td>
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<td>binders</td>
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<tr>
<td>TBW</td>
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<tr>
<td>litres</td>
<td>0.199</td>
<td>0.049</td>
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Table 2: Multiple linear regression analysis for indoxylsulfate (IS) and p-cresyl sulfate (PCS). Residual renal function (RRF - combined 24 hour urinary urea and creatinine clearance). C reactive protein (CRP), prescription HMG CoA 3 reductase inhibitor (statin). Standard error of β (SE), confidence limits (CL). ICS model corrected $r^2 = 0.179$, and PCS, $r^2 = 0.235$

<table>
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<tr>
<th></th>
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<th>t</th>
<th>95% CL</th>
<th>F</th>
<th>p</th>
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<td>albumin</td>
<td>4.31</td>
<td>1.1</td>
<td>4.02</td>
<td>2.2 to 6.4</td>
<td>16.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Variable</td>
<td>Non vegetarian</td>
<td>Vegetarian</td>
<td>P value</td>
<td></td>
<td></td>
<td></td>
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<td>------------</td>
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<td></td>
</tr>
<tr>
<td>Age yr</td>
<td>63.7 ±16.9</td>
<td>71.7 ±11.6</td>
<td>0.07</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male %</td>
<td>59.0</td>
<td>68.8</td>
<td>X2=0.5, p&gt;0.5</td>
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</tbody>
</table>

Table 3: Patient demographics of those who were vegetarian and those who were non-vegetarian. Serum values pre mid-week dialysis session, and body composition postdialysis. Extra cellular water (ECW) total body water (TBW), Residual renal function (RRF - combined 24 hour urinary urea and creatinine clearance), C reactive protein (CRP). Chi square (X2)
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<td>Diabetic %</td>
<td>55.7</td>
<td>68.9</td>
<td>X²=0.27, p&gt;0.5</td>
</tr>
<tr>
<td>Vintage months</td>
<td>25.7 (13.5-62)</td>
<td>29.8 (10.9-69.2)</td>
<td>0.97</td>
</tr>
<tr>
<td>RRF ml/min 1.73m²</td>
<td>0 (0-2.2)</td>
<td>0 (0-1.2)</td>
<td>0.23</td>
</tr>
<tr>
<td>Weight kg</td>
<td>71.7 ±18.1</td>
<td>65.6 ±12.1</td>
<td>0.20</td>
</tr>
<tr>
<td>BMI kg/m²</td>
<td>26.5 ± 6.0</td>
<td>25.4 ± 5.2</td>
<td>0.50</td>
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<tr>
<td>ECW/TBW</td>
<td>0.394 ±0.022</td>
<td>0.399 ±0.016</td>
<td>0.39</td>
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<td>Haemoglobin g/l</td>
<td>109.3 ±17.8</td>
<td>116.1 ±12.9</td>
<td>0.15</td>
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<tr>
<td>Albumin g/l</td>
<td>39.4 ±4.3</td>
<td>38.7 ±3.5</td>
<td>0.53</td>
</tr>
<tr>
<td>Urea mmol/l</td>
<td>18.4 ±5.2</td>
<td>13.8 ±3.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Creatinine umol/l</td>
<td>699 ±258</td>
<td>503 ±115</td>
<td>&lt;0.01</td>
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<tr>
<td>Phosphate mmol/l</td>
<td>1.58 ±0.45</td>
<td>1.33 ±0.21</td>
<td>0.02</td>
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<tr>
<td>Cholesterol mmol/l</td>
<td>3.96 ±1.25</td>
<td>3.56 ±0.96</td>
<td>0.22</td>
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<tr>
<td>LDL cholesterol mmol/l</td>
<td>2.06 ±0.93</td>
<td>1.60 ±0.79</td>
<td>0.06</td>
</tr>
<tr>
<td>CRP mg/l</td>
<td>6.5 (2-13)</td>
<td>4 (1.3-8.3)</td>
<td>0.17</td>
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<tr>
<td>B2 microglobulin mg/l</td>
<td>28.2 (22.5-34.5)</td>
<td>25.1 (17.1-32.3)</td>
<td>0.09</td>
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<tr>
<td>Urea reduction ratio</td>
<td>73.3 ±7.4</td>
<td>73.8 ±7.8</td>
<td>0.81</td>
</tr>
<tr>
<td>Sessional Kt/V&lt;sub&gt;urea&lt;/sub&gt;</td>
<td>1.55 ±0.32</td>
<td>1.58 ±0.35</td>
<td>0.74</td>
</tr>
<tr>
<td>Session time h</td>
<td>3.64 ±0.53</td>
<td>3.59 ±0.52</td>
<td>0.73</td>
</tr>
<tr>
<td>Convection volume L</td>
<td>15.2 ±2.3</td>
<td>16.5 ±3.7</td>
<td>0.13</td>
</tr>
<tr>
<td>G N/kg/day</td>
<td>1.62 ±0.49</td>
<td>1.25 ±0.28</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
Conflicts of interest
Neither author has any conflict of interest

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