In this study, we compared changes in inflammatory markers—C-reactive protein (CRP), pentraxin 3 (PTX3), serum component of amyloid A (SAA), and procalcitonin (PCT)—in 182 subjects: 69 from the general population (GP), 47 with CKD, 19 with an implanted intra-abdominal catheter for peritoneal dialysis (“prePD”), and 47 on peritoneal dialysis (PD). These were the results [median (95% confidence interval)] for the GP, CKD, prePD, and PD groups respectively:

- **CRP:** 1.40 mg/L (1.15 – 2.10 mg/L), 5.30 mg/L (3.04 – 8.06 mg/L), 3.33 mg/L (2.15 – 12.58 mg/L), 7.25 mg/L (4.43 – 15.16 mg/L)
- **SAA:** 3.10 mg/L (2.90 – 3.53 mg/L), 7.77 mg/L (4.17 – 15.83 mg/L), 7.30 mg/L (4.81 – 10.96 mg/L), 9.14 mg/L (5.31 – 23.54 mg/L)
- **PCT:** 0.028 ng/mL (0.022 – 0.032 ng/mL), 0.121 ng/mL (0.094 – 0.166 ng/mL), 0.160 ng/mL (0.090 – 0.277 ng/mL), 0.363 ng/mL (0.222 – 0.481 ng/mL)
- **PTX3:** 0.54 ng/mL (0.33–0.62 ng/mL), 0.71 ng/mL (0.32–1.50 ng/mL), 0.56 ng/mL (0.44–1.00 ng/mL), 1.04 ng/mL (0.65–1.56 ng/mL)

After catheter insertion, CRP showed a nonsignificant declining trend that disappeared throughout PD. The behavior of SAA was similar to that of CRP and was not modified by the changes induced by the start of PD. An increase in PTX3 was observed only with PD, which may be related to a local proinflammatory state caused by PD solution. We can conclude that catheter insertion for PD does not account for most of the local inflammatory changes observed in PD patients.

Key words
Abdominal catheter insertion, inflammation markers, pentraxin, serum component of amyloid A

Introduction
Recently, several reports evaluating the inflammatory response in peritoneal dialysis (PD) and focusing on the associated markers have been published. Our group studied various components involved in the inflammatory process—C-reactive protein (CRP), pentraxin 3 (PTX3), serum component of amyloid A (SAA), and procalcitonin (PCT)—at various stages, from end-stage renal disease to the beginning of PD.

The pentraxins are a group of proinflammatory proteins (humoral innate immune response) with a radially symmetric pentameric ring. There are two pentraxin classes: the short pentraxins such as CRP, and the long pentraxins such as PTX3. C-Reactive protein, which is produced and released by the liver (directly induced by interleukin 6), binds to phosphocholine in the presence of calcium and plays an important role in direct recognition of pathogens and phospholipid constituents of damaged cells. The rapidity of the CRP response makes this molecule an acute-phase reactant. Pentraxin 3 is thought to have an important role as a regulator of innate immunity, innate resistance against pathogens, regulation of inflammatory reactions (important in the activation of complement, facilitating pathogen recognition, and acting as a predecessor of antibodies) and the elimination of apoptotic cells (1,2). It is synthesized, at a locoregional level, by endothelial dendritic cells, smooth muscle, fibroblasts, neutrophils, monocytes, and macrophages in response to inflammatory stimuli (interleukin 1, tumor necrosis factor α, oxidized low-density lipoprotein cholesterol) and to microorganisms (3,4), and it is also synthesized in kidney proximal tubular epithelial cells, mesangial cells, and renal fibroblasts (5–7).
Synthesized in the liver, SAA is an acute-phase reactant that binds to phospholipids and proteins. Its level rises in several inflammatory processes, and not being affected by renal function, it can be determined in oliguric or anuric patients (8,9).

Procalcitonin is a protein whose levels increase (induced by tumor necrosis factor α) specifically from the second hour of a bacterial infection. When sepsis resolves, serum levels of PCT return to normal. Procalcitonin is an important aid in differentiating between bacterial infection and other causes of inflammatory reactions (10,11). Recently, PCT has been considered a marker useful for the evaluation of micro-inflammation and the biocompatibility of hemodialysis membranes in hemodialysis patients without infection (12). Values of PCT decline as membrane biocompatibility increases.

Similarly, PD can stimulate or worsen the inflammatory state of PD patients. In the present study, we set out to describe and analyze changes in these emerging markers of innate immune and inflammatory response in a variety of subjects: a group from the general population of the Cantabrian Health Service (GP) as controls, a group of end-stage chronic kidney disease (CKD) patients, a group of CKD patients with an implanted intra-abdominal catheter for peritoneal dialysis (“prePD”), and a group that had been on PD for more than 1 month.

Methods
We obtained serum and EDTA plasma from 182 subjects: 69 from the GP; 47 patients with stage IV or V CKD [estimated glomerular filtration rate (eGFR) determined using the Modification of Diet in Renal Disease (MDRD4) formula] not on renal replacement therapy; 19 prePD (≥3 weeks after catheter implantation); and 47 on PD. All were associated with the Nephrology Department of University Hospital “Marqués de Valdecilla” and had no infection at the time of the blood draw. An EDTA plasma sample was available only from approximately 20 patients in each group.

In all cases, these serum biomarkers were quantified: serum creatinine (sCr) by the Jaffe method on a Dimension RXL analyzer (Siemens Healthcare, Mannheim, Germany); standardized CRP, SAA, and cystatin C (CysC) by immunonephelometry (CardioPhase High Sensitivity C-Reactive Protein and N Latex SAA and Cystatin C kits) on a Behring Nephelometer II (Siemens Healthcare); serum PCT by immunoassay (Brahms PCT-sensitive Kryptor assay: Brahms, Hennigsdorf, Germany); and plasma PTX3 by ELISA (Human Pentraxin3/TSG-14 ELISA System: Perseus Proteomics, Tokyo, Japan).

The statistical treatment of data (Mann–Whitney U-test, with significance set at \( p < 0.050 \)) was carried out using the MedCalc software application (MedCalc, Ghent, Belgium).

Results
The levels of all inflammatory markers have a non-parametric distribution, and so results are expressed as medians with 95% confidence intervals (CIs). Table I shows the results.

Serum creatinine was determined to select the subjects and to confirm their eGFR by MDRD4. The sCr and CysC can be seen to increase as renal insufficiency evolves. Serum CRP was higher in all groups with a lower eGFR, but was significant \( (p < 0.050) \) only between the control (GP) group and the CKD groups (with or without renal replacement therapy). In comparisons of the CKD and PD groups, an increasing trend in CRP level (nonsignificant) was observed, with a declining trend (nonsignificant) after catheter insertion that disappeared when PD started.

Levels of SAA changed in a manner similar to levels of CRP, but SAA was not modified by the changes induced by PD. Compared with levels in the control group, SAA levels were elevated \( (p < 0.050) \) in all groups with chronic impairment of eGFR. In the prePD group, levels of SAA changed in a manner similar to levels of CRP.

Compared with the GP group, all CKD groups had significant differences in PCT level. The increased level in CKD persisted in prePD (nonsignificantly different, but at the upper limit, nearing a diagnosis of infection). However, between the non-PD CKD groups and the PD patients, the differences in PCT level were significant.

Plasma PTX3 increased only in end-stage CKD patients on PD. Its plasma concentration did not significantly change, not even with catheter insertion, until the beginning of PD therapy (Figure 1).

Discussion and conclusions
In the present study, we observed that levels of CRP, PTX3, SAA, and PCT, which are markers of inflammation, are elevated in individuals with CKD.
<table>
<thead>
<tr>
<th>Variable</th>
<th>GP (n=69)</th>
<th>CKD (n=47)</th>
<th>PrePD (n=19)</th>
<th>PD (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>69</td>
<td>47</td>
<td>19</td>
<td>47</td>
</tr>
<tr>
<td>sCr (mg/dL)b</td>
<td>0.91 (0.88 to 0.95)</td>
<td>4.61 (4.15 to 5.08)</td>
<td>5.61 (4.75 to 6.48)</td>
<td>8.07 (7.34 to 8.81)</td>
</tr>
<tr>
<td>CysC (mg/L)b</td>
<td>0.81 (0.75 to 0.86)</td>
<td>3.29 (3.07 to 3.51)</td>
<td>3.96 (3.64 to 4.30)</td>
<td>5.73 (4.99 to 6.46)</td>
</tr>
<tr>
<td>CRP (mg/L)c</td>
<td>1.40 (1.15 to 2.10)</td>
<td>5.30 (3.04 to 8.06)d</td>
<td>3.33 (2.15 to 12.58)d</td>
<td>7.25 (4.43 to 15.16)d</td>
</tr>
<tr>
<td>SAA (mg/L)c</td>
<td>3.10 (2.90 to 3.53)</td>
<td>7.77 (4.17 to 15.83)d</td>
<td>7.30 (4.81 to 10.96)d</td>
<td>9.14 (5.31 to 23.54)d</td>
</tr>
<tr>
<td>PCT (ng/mL)c</td>
<td>0.028 (0.022 to 0.032)</td>
<td>0.121 (0.094 to 0.166)d,e</td>
<td>0.160 (0.090 to 0.277)d,e</td>
<td>0.363 (0.222 to 0.481)d,e,f,g</td>
</tr>
<tr>
<td>PTX3 (ng/mL)c</td>
<td>0.54 (0.33 to 0.62)</td>
<td>0.71 (0.32 to 1.50)</td>
<td>0.56 (0.44 to 1.00)d</td>
<td>1.04 (0.65 to 1.56)d,g</td>
</tr>
</tbody>
</table>

\( n = 20 \) for GP, \( n = 15 \) for CKD, \( n = 19 \) for PrePD, \( n = 25 \) for PD.

\( a \) With abdominal catheter, but dialysis not started.
\( b \) Mean (95% confidence interval).
\( c \) Median (95% confidence interval).
\( d \) \( p < 0.050 \) compared with the GP.
\( e \) \( p < 0.050 \) compared with the PD population.
\( f \) \( p < 0.050 \) compared with the CKD population.
\( g \) \( p < 0.050 \) compared with the prePD population.
\( h \) Sample sizes are different because of difficulty in collecting an additional EDTA tube.

sCr = serum creatinine; CysC = cystatin C; CRP = C-reactive protein; SAA = serum component of amyloid A; PCT = procalcitonin; PTX3 = pentraxin 3.

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**Figure 1**  Number of times that each determination exceeded the upper reference limit (URL). The URLs were, for C-reactive protein (CRP), 10.00 mg/L (acute inflammation); for pentraxin-3 (PTX3), 1.18 ng/mL; for serum component of amyloid A (SAA), 6.40 mg/L; and, for procalcitonin (PCT), 0.200 ng/mL (within the limits for a diagnosis of local infection). GP = general population; CKD = chronic kidney disease population; pre_PD = pre-peritoneal dialysis population; PD = peritoneal dialysis population.
Those data support the proinflammatory state of CKD patients.

We also observed that, compared with levels in the inflammatory state of CKD, the markers CRP, SAA, and PTX3 all dropped slightly after implantation of the peritoneal catheter. It is possible that patients having a catheter, but not yet on dialysis, either experienced a spontaneous improvement of inflammatory status or maintained better compliance with previous therapeutic recommendations.

However, it was the dialysis process that caused real inflammatory changes. For those on PD, compared with the prePD group, all inflammatory markers increased, nonsignificantly for CRP and SAA, but significantly for PCT and PTX3.

The increase in a locoregional inflammation marker such as PTX3 (3,4), together with the similar increase in PCT (12), probably shows that PCT has a role as a marker of micro-inflammation, possibly answering the question of whether a state of local inflammation related directly to PD occurs. By contrast, insertion of a catheter (prePD) does not account for the most of the local inflammatory changes observed in PD patients. Osmotic fluids for PD may perhaps be the cause of this inflammatory state.

Interestingly, the changes in PCT level have attracted our attention, because in the absence of infection, the magnitude of the fluctuations in this marker approach reference levels for a diagnosis of local infection (0.100 – 0.500 ng/mL). We have to conclude that PCT in CKD patients must be carefully evaluated. We suggest that, although significantly elevated PCT concentrations offer good sensitivity and specificity for an early diagnosis of systemic bacterial infection (13), there is a need to establish new reference values for the proper classification of local infection, systemic inflammatory response syndrome, and sepsis in CKD patients on PD.

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Disclosures
The authors have no conflicts of interest to declare.

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