Procalcitonin and minimal-change nephropathy: a pilot study

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INTRODUCTION
This study assessed the role of procalcitonin (PCT) in the differentiation of minimal-change nephropathy (MCN) relapses from infections co-existent with proteinuria flares in children.

METHODS
Data on the PCT levels of patients with MCN who were on follow-up were retrospectively gathered at relapse (Group I), during proteinuria attacks co-existent with intercurrent infection (Group II) and at remission (Group III). The results of these three groups were then prospectively compared with nephrologically healthy patients who had infections that were similar to those in Group II (Group IV), and controls (Group V).

RESULTS
Significant differences in PCT level were noted between patients of Groups I, II and IV and the other two groups. A 93% reduction in proteinuria was achieved for Group II patients following an antibiotic regimen. The difference in PCT level between Groups I and II was significant. PCT showed a higher diagnostic predictability than C-reactive protein (CRP) in Group I patients, and was as good as CRP for those with infection and infection-related proteinuria. Sensitivity × specificity in relapse and infection-related states for PCT were 0.472 and 0.628, respectively, and those for CRP were 0.183 and 0.762, respectively.

CONCLUSION
A combined approach with CRP and PCT readings may be beneficial in discriminating proteinuria attacks co-existent with intercurrent infection from sole relapses of nephrotic syndrome. PCT may be a part of the wide spectrum of immune abnormalities seen in patients with MCN.

Keywords: C-reactive protein, children, infection, minimal change nephropathy, procalcitonin, proteinuria

Data on PCT, ESR, CRP and proteinuria were gathered retrospectively from the patient records for Group I–III (levels measured at the time of admission) patients and those for Group IV and V patients were measured prospectively. The ESR, CRP and PCT levels were harvested from the same blood samples. 10 ml venous blood was drawn and centrifuged at 3,000 rpm for 30 minutes for PCT and CRP measurements. CRP levels were measured by the turbidimetric method using a photometer (Biosystems SA, Barcelona, Spain) and levels < 6 mg/L were accepted as normal for this assay. Serum PCT levels were detected using an immunoluminometric assay (LUMItest®; BRAHMS Aktiengesellschaft, Henningsdorf, Germany), which relied on forming sandwich complexes for the principal measurement of PCT levels in samples. While the analytical assay sensitivity of PCT is approximately 0.1 ng/ml, its functional assay sensitivity (20% interassay variation coefficient) is approximately 0.3 ng/ml.

All statistical analyses were performed using the Statistical Package for the Social Sciences version 15.0 (SPSS Inc, Chicago, IL, USA). The Kruskal-Wallis and chi-square tests were performed in the groups for obtaining the non-Gaussian distribution of age and gender, respectively. For equal distribution, data was expressed as mean ± standard deviation (SD) and the Mann-Whitney U-test was used for comparison of means. A p-value < 0.05 was considered statistically significant. The chi-square values on logistic regression analysis of patients in Groups I and II were maintained to compare the predictability of PCT and CRP. The optimal cut-offs for predicting relapse or infection-induced proteinuria were investigated using receiver operating characteristic (ROC) analysis, and diagnostic accuracy was assessed from the area under the ROC curves.

RESULTS
Groups I, II and III (mean age 8 ± 5 years) were constituted from the data of 12 girls and 22 boys with MCN. The p-value was > 0.05 for these groups by the Kruskal-Wallis and chi-square tests. An analysis of the results of the acute phase reactant levels (Table I) showed that mean PCT levels were significantly different between Groups I and II (p < 0.05). The results for Groups I and II were significantly different from those of Groups III and V (p < 0.05). However, the levels were not significantly different between Groups III and V. With respect to CRP, there was no significant difference among Groups I, III and V (p > 0.05).

All Group II patients developed proteinuria when in remission. All patients were on a maintenance immunosuppression regimen except for seven patients in this group. The mean white blood cell (WBC) count was 12.1 ± 3.2 x 10⁴/mm³, with 75% neutrophilia. All patients were on a maintenance immunosuppression regimen; not only for the 23 patients with PCT ≥ 2 ng/ml but also for the three patients with PCT of 1–2 ng/ml (26/28; 93%). The two resistant patients in Group II were considered as relapers (7%).

Logistic regression analysis (Table II) indicated that although the chi-square value for PCT was higher than that for CRP in Group I, this was not the case for patients in Group II. The overall predicted percentages for patients in Groups I and II were: Group I (PCT 96.1%; CRP 64.5%) and Group II (PCT 70.9%; CRP 66.0%). The optimal cut-offs for predicting relapse or infection-induced proteinuria by the ROC test (Table III) showed that the diagnostic predictability of PCT was higher than that of CRP in patients who relapse, but was approximately equal for PCT and CRP in those with infections and infection-related proteinuria.

DISCUSSION
A wide variety of immunological abnormalities that affect both humoral and cellular immunity has been described in patients with MCN, with tumour necrosis factor-α (TNF-α) being one of the variables. Therefore, there is a possibility that due to the rapid and specific induction of TNF-α following adequate stimulus, PCT may have a pathophysiological function in acute immune response. T-cells are the other potential immunological

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### Table I. Laboratory findings.

<table>
<thead>
<tr>
<th>Group</th>
<th>ESR (mm/hr)</th>
<th>PCT (ng/ml)</th>
<th>CRP (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>53.18 ± 34.5</td>
<td>0.92 ± 0.36</td>
<td>2.1 ± 0.2</td>
</tr>
<tr>
<td>Group II</td>
<td>60.0 ± 20.0</td>
<td>2.4 ± 1.4</td>
<td>15.0 ± 5.0</td>
</tr>
<tr>
<td>Group III</td>
<td>28.42 ± 15.7</td>
<td>0.35 ± 0.05</td>
<td>3.0 ± 0.5</td>
</tr>
<tr>
<td>Group IV</td>
<td>80.0 ± 28.0</td>
<td>4.0 ± 2.0</td>
<td>20.0 ± 10.0</td>
</tr>
<tr>
<td>Group V</td>
<td>13.65 ± 7.35</td>
<td>0.35 ± 0.01</td>
<td>2.0 ± 0.1</td>
</tr>
</tbody>
</table>

* Relapse (n = 26); Proteinuria coexistent with intercurrent infection (n = 28); Remission (n = 25); Infection (n = 25); Control (n = 25)

* ESR: erythrocyte sedimentation rate; PCT: procalcitonin; CRP: C-reactive protein

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**Fig. 1.** Infection foci among patients of Groups II and IV.
partner in MCN. CD4 regulatory cells, classified as Th1 and Th2 cells according to their cytokine secretion patterns, have important roles to play – Th1 cells mediate several functions related to cytotoxicity and local inflammatory reactions, while Th2 cells stimulate B-cells to produce antibodies (IgE, IgA, IgG4), promote eosinophil proliferation and the development of allergic responses. Plausible mechanisms whereby a type 2 (Th2) cytokine bias could directly or indirectly cause MCN have been reported. In addition, PCT elevations have been noticed in systemic inflammatory syndromes where the Th1/Th2 balance is in favour of Th2 in non-septic patients, such as those with major trauma and cardiopulmonary bypass. Therefore, one of the aims of this study was to investigate the role of PCT in MCN pathogenesis. We found that the PCT levels were significantly different in patients in relapse, and hence, it is possible that PCT has a pro-inflammatory or non-infectious systemic inflammatory cytokine-like mediator role in MCN immunopathogenesis and that the Th1/Th2 balance was in favour of Th2. However, this observation needs to be confirmed by future studies.

Although the range of PCT is generally defined as 1–2 ng/ml, PCT levels of 2–1,000 ng/ml have been known to exist during bacterial infections. False negative results may be caused by localised bacterial infections, type of causative agent (virus or bacteria), infections where other inflammatory pathways are activated (Lyme disease or tuberculosis) or the short half-life of PCT (22 hours). Nonetheless, PCT, ESR and CRP have all been accepted as indicators of infection. Infections co-existing with proteinuria were mostly diagnosed using clinical and laboratory methods, and the prognosis monitored through an improvement of proteinuria following antibiotic treatment in our study. Not surprisingly, findings on infection based on the levels of PCT, ESR and CRP, and especially those between CRP and PCT, were found to be concordant.

We found that proteinuria was reduced in not only most Group II patients with PCT ≥ 2 ng/ml but also in those with PCT of 1–2 ng/ml (or lower than that seen in bacterial infections). The reasons for this may be varied, as detailed above, and may include atypical bacterial or viral infections (due to the effect of antibiotics or the self-limiting course of viral infections) and the short half-life of PCT. On the other hand, the persistence of proteinuria despite antibiotic treatment in patients with PCT > 2 ng/ml (the range for bacterial infection) may suggest that the triggered immune mechanisms leading to proteinuria were so effective that the emergence of MCN could not be prevented by antibiotic treatment only and thereby, may highlight the need for immunosuppressants in such patients as for those in relapse.

CRP is a cytokine-induced acute-phase protein whose blood levels rise during an unspecific response to infection or non-infectious inflammatory processes. It often exceeds normal threshold levels within 4–8 hours of an acute inflammatory event. However, the results of our study indicate that CRP, as a measure, may not be as effective as PCT in predicting relapse and is least useful in predicting the course of MCN. In contrast, a study by Wasilewska et al reported that increased high sensitive-CRP (hs-CRP) levels were seen in relapses of childhood steroid-sensitive nephrotic syndromes and after cyclosporine A treatment in patients with MCN. Such divergence in findings may probably be due to the testing of hs-CRP in Wasilewska et al’s study or even the histopathology of their participants (renal biopsy, 8/20; minimal-change nephrotic syndrome, 5/8). Interestingly, some studies have reported that CRP was not affected by nephrotic syndrome activity

Table II. Logistic regression analysis of CRP and PCT levels among patients of Groups II and IV.

<table>
<thead>
<tr>
<th>Group</th>
<th>OR* (95% CI)</th>
<th>p-value</th>
<th>Chi-square test</th>
<th>p-value</th>
<th>Predictability percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group Ia</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>PCT</td>
<td>5.3952 (0.0002–140812.315)</td>
<td>0.001</td>
<td>67.769</td>
<td>&lt; 0.001</td>
<td>96.1</td>
</tr>
<tr>
<td>CRP</td>
<td>0.7719 (0.1371–4.3452)</td>
<td>0.003</td>
<td>16.109</td>
<td>&lt; 0.001</td>
<td>64.5</td>
</tr>
<tr>
<td>Group IIb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCT</td>
<td>1.0189 (0.824–1.2599)</td>
<td>0.083</td>
<td>2.974</td>
<td>0.085</td>
<td>70.9</td>
</tr>
<tr>
<td>CRP</td>
<td>1.0072 (0.9603–1.0565)</td>
<td>0.003</td>
<td>9.362</td>
<td>0.002</td>
<td>66.0</td>
</tr>
</tbody>
</table>

* Per 0.1 unit increase; a Relapse; b Proteinuria coexistent with intercurrent infection

OR: odds ratio; CI: confidence interval; PCT: procalcitonin; CRP: C-reactive protein

Table III. Cut-off values for PCT and CRP as per ROC analysis.

<table>
<thead>
<tr>
<th>Group</th>
<th>AUC* (95% CI)</th>
<th>p-value</th>
<th>Cut-off value*</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Sensitivity × specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>PCT</td>
<td>0.726 (0.596–0.858)</td>
<td>0.030</td>
<td>0.385</td>
<td>0.962</td>
<td>0.491</td>
<td>0.472</td>
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<tr>
<td>CRP</td>
<td>0.279 (0.168–0.391)</td>
<td>0.002</td>
<td>2.065</td>
<td>0.539</td>
<td>0.340</td>
<td>0.183</td>
</tr>
<tr>
<td>Proteinuria coexistent with intercurrent infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCT</td>
<td>0.759 (0.667–0.851)</td>
<td>0.000</td>
<td>1.215</td>
<td>0.857</td>
<td>0.733</td>
<td>0.628</td>
</tr>
<tr>
<td>CRP</td>
<td>0.839 (0.772–0.906)</td>
<td>0.000</td>
<td>5.12</td>
<td>1.000</td>
<td>0.762</td>
<td>0.762</td>
</tr>
</tbody>
</table>

* With highest sensitivity × specificity; ^ Group I vs. Groups III–V; * Groups II–IV vs. Groups III–V

AUC: area under curve; CI: confidence interval; PCT: procalcitonin; CRP: C-reactive protein
in invasive bacterial diseases. We found that the diagnostic predictability of both PCT and CRP was comparable for MCN patients with infection-induced or co-existent proteinuria. However, the predictability of CRP was slightly superior to that of PCT in patients with infection-induced proteinuria. The latter finding may be associated with the relative half-lives of these two parameters in blood.

In conclusion, both CRP and PCT may be needed, with varying cut-off values, for a complete differentiation of patients with infection co-existent proteinuria flares and those in relapse. A combined approach with both CRP and PCT readings may be more sensitive. The initiation of appropriate antibiotic treatment based on clinical findings and monitoring of both PCT and CRP levels may help to reduce proteinuria, and thus avoid unnecessary treatment with immunosuppression drugs. Our results also suggest that PCT irregularities may be part of a wide spectrum of immune abnormalities seen in patients with MCN. The role of PCT in MCN, however, needs further extensive examination and will be the focus of future studies.

REFERENCES