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Urinary prednisolone excretion is a determinant of serum hepcidin levels in renal transplant recipients

To the Editor:
Hepcidin, which is synthesized and secreted by the liver, is considered the master regulator of iron homeostasis. Hepcidin regulates the amount of iron absorbed from the intestines and the iron release from the reticuloendothelial system by degrading ferroportin, the iron transporter located at the duodenal enterocytes and macrophages. Circulating levels of hepcidin are known to be controlled by available iron stores, inflammation, hypoxia, insulin levels, and erythropoiesis.

REFERENCE
Recently, hepcidin antagonists have been introduced as potential treatment to improve iron-restrictive anemia. By improving iron availability and subsequently hemoglobin levels, hepcidin antagonists might be able to improve quality of life and outcome in different patient settings. Therefore, all factors that affect serum hepcidin levels are clinically relevant specifically in populations where in the future the use of hepcidin antagonists may be considered. It has already been established that both testosterone\(^1\) and estrogens\(^2\) are associated with suppression of serum hepcidin in men. On the other hand progesterone, the anabolic steroid epitostanol, as well as the progesterone antagonist, mifepristone, are included patients with missing data on serum hepcidin (\(b=0.12, P<.001\)). After adjustment for high-sensitivity C-reactive protein (eGFR) compared to those within the other two tertiles. Furthermore, higher hemoglobin, lower hepcidin, and lower ferritin levels were noted in RTRs in the highest tertile of prednisolone exposure compared to RTRs in the other two tertiles (Table 1).

In univariate regression analysis, serum hepcidin was found to be negatively associated with 24-h urinary prednisolone excretion (\(b=-0.15, P<.001\)). After adjustment for high-sensitivity C-reactive protein (hs-CRP), hepcidin remained associated with prednisolone (\(b=-0.13, P=.002\)). Further adjustment for eGFR did not materially alter this association (\(b=-0.12, P=.006\)). When including prednisolone in a backward multivariate model with age, sex, eGFR, ferritin, hemoglobin, erythropoietin, and insulin, prednisolone remained an independent determinant of hepcidin (\(b=-0.10, P=.001\)), besides expected relationships of hepcidin with ferritin, hs-CRP, erythropoietin and insulin. In addition, serum hepcidin was found to be a determinant of hemoglobin levels (\(b=-0.08, P=.03\)) independently of age, sex, and eGFR.

In this study, we show that 24-h urinary prednisolone excretion is negatively associated with serum hepcidin in RTRs irrespective of potential confounders, including eGFR. All RTRs in our cohort used a low dose

### TABLE 1  Baseline characteristics of 551 renal transplant recipients according to tertiles of 24-h urinary prednisolone excretion

<table>
<thead>
<tr>
<th>Variables</th>
<th>All patients</th>
<th>Tertiles of urinary prednisolone excretion (pmol/24 h)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>T1 (125–371)</td>
<td>T2 (619–904)</td>
</tr>
<tr>
<td>Urinary prednisolone (pmol/24 h)</td>
<td>758 (371–1278)</td>
<td>256 (125–371)</td>
<td>755 (619–904)</td>
</tr>
<tr>
<td>General characteristics</td>
<td></td>
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<tr>
<td>Age (years)</td>
<td></td>
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<tr>
<td>Male sex (n %)</td>
<td></td>
<td></td>
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<tr>
<td>eGFR (mL/min/1.73 m(^2))</td>
<td></td>
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<tr>
<td>Laboratory parameters</td>
<td></td>
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<tr>
<td>Hepcidin (ng/mL)</td>
<td>7.2 (3.3–13.5)</td>
<td>8.6 (4.3–14.3)</td>
<td>7.0 (2.8–14.3)</td>
</tr>
<tr>
<td>Ferritin (g/L)</td>
<td>13.8 ± 1.6</td>
<td>13.6 ± 1.6</td>
<td>13.8 ± 1.6</td>
</tr>
<tr>
<td>EPO (IU/L)</td>
<td>17.4 (12.0–24.3)</td>
<td>17.7 (11.8–25.4)</td>
<td>17.9 (13.0–24.3)</td>
</tr>
<tr>
<td>hs-CRP (mg/L)</td>
<td>2.0 (0.8–4.8)</td>
<td>2.1 (1.0–5.1)</td>
<td>2.7 (0.9–4.8)</td>
</tr>
<tr>
<td>Insulin (µU/mL)</td>
<td>11.1 (7.9–16.3)</td>
<td>11.4 (7.8–17.5)</td>
<td>11.2 (8.3–15.1)</td>
</tr>
</tbody>
</table>

eGFR, estimated glomerular filtration rate; EPO, erythropoietin; hs-CRP, high sensitivity C-reactive protein.
prednisolone (5–10 mg/day). Remarkably, this resulted in a broad range of 24-h urinary prednisolone excretion and a modest association with the daily prednisolone dose, in keeping with considerable inter-subject pharmacokinetic variability. Twenty-4 h urinary prednisolone excretion is considered to reflect the overall exposure to prednisolone. Previously, it has been shown that prednisolone dose-dependently inhibits the release of interleukin-6 (IL-6) which is known to induce hepcidin expression. We had no data available on IL-6 levels to assess whether effects on IL-6 is the mechanism behind the association of prednisolone with hepcidin. The possible role of prednisolone as a direct hepcidin antagonist and possible mechanisms linking prednisolone with hepcidin need to be delineated in more detail in future studies.

The major strength of this report is the large cohort of RTRs with availability of concurrent 24-h urinary prednisolone excretion and hepcidin data. Limitations are that it comprises a single center study, and that we cannot exclude the possibility of residual confounding.

In conclusion, lower serum hepcidin levels are related to higher 24-h urinary prednisolone excretion in RTRs independent of clinically relevant covariates. Our findings extend earlier data concerning effects of other (synthetic) steroids on hepcidin regulation, and provide a rationale to more precisely delineate direct or indirect effects of glucocorticoids on hepcidin regulation. From a clinical perspective, our findings lend support to the possibility that prednisolone may be regarded as a hitherto unappreciated hepcidin antagonist.

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CONFLICT OF INTEREST
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REFERENCES

Characterization of TP53 mutations in clonal cytopenia of undetermined significance

To the Editor:
The diagnosis of myelodysplastic syndrome (MDS) requires persistent cytopenia with at least one of the following criteria: dysplasia in at least 10% of cells in any hematopoietic lineage, increased myeloblasts (5–19%) in bone marrow (or 2–19% myeloblast in peripheral blood), or MDS defining cytogenetic abnormalities. Some patients have cytopenia and/or gene mutations, but do not meet other criteria of MDS. These pre-MDS conditions include idiopathic cytopenia of undetermined significance (ICUS), clonal hematopoiesis of indeterminate potential (CHIP) and clonal cytopenia of undetermined significance (CCUS). The mutations frequently identified in these pre-MDS conditions, including DNMT3A, TET2, and ASXL1, are also the common mutations detected in MDS. ICUS, CHIP, and CCUS all carry an increased risk for progression to MDS. The rate of progression to MDS varies, likely depending on the specific genes that are mutated and their mutation burden. The role of each individual mutation in disease progression is not well characterized.

TP53 is a tumor suppressor gene that has been studied extensively in MDS and AML, in which the mutations are associated with a complex karyotype and a poor prognosis. Its mutations also occur in CHIP and CCUS. The characteristics of TP53 mutations and their role in disease progression in these pre-MDS conditions are unknown. In this study, we aim to characterize the clinicopathological features of CCUS cases associated with TP53 mutations.