(Belo Horizonte), Instituto do Câncer do Estado de São Paulo (São Paulo), Santa Casa de Misericórdia de Santos (Santos), Santa Casa de Misericórdia de São Paulo (São Paulo), Universidade Estadual de Campinas (Campinas), Universidade Estadual de Londrina (Londrina), Universidade Federal de Goiás (Goiânia), Universidade Federal de Minas Gerais (Belo Horizonte), Universidade Federal de São Paulo (São Paulo), Universidade Federal do Ceará (Fortaleza), Universidade Federal do Paraná (Curitiba), Universidade Federal do Rio de Janeiro (Rio de Janeiro). We would also like to thank José Márcio Duarte and the staff from Departamento de Informática em Saúde - UNIFESP for providing technical support.

CONFLICT OF INTEREST
The authors have no conflicts of interest to declare.

Matheus Vescovi Gonçalves1,2, Celso Arrais Rodrigues1,2,3, Irene Gyongyver Heidemarie Lorand Metze3, Marcelo Pitombeira Lacerda4, Maria de Lourdes Lopes Ferrari Chauffaille1, Aíza Azevedo5, Cintia Machado6, Carlos Sérgio Chiattone7,8, Sérgio Fortier5,9, Leila Perobelli7, Maura Rosane Valerio Ikoma8, Nelma Clementino9, Danielle Leão Cordeiro de Farias10, Fernando Barroso Duarte11, Valeria Buccheri12, Ana Paula de Azambuja12, Denise Ramos de Almeida13, Vera Lucia Piratininga Figueiredo11, Larissa Veloso Mendes Ommati12, Young Ok Lee13, Leila Perobelli7, Sérgio Fortier5,6,7, Vivia Machado Sthel11, Nelson Hamerschlak10, Vivia Machado Sthel11, Mihoko Yamamoto1

1Universidade Federal de São Paulo (UNIFESP/EPFM), São Paulo, Brazil
2Hospital Sírio Libanes, São Paulo, Brazil
3University of Campinas, Campinas, Brazil
4Hemocentro de Pernambuco, Hemope, Recife, Brazil
5Santa Casa de Misericórdia de São Paulo, São Paulo, Brazil
6Hospital Samaritano, São Paulo, Brazil
7Hospital de Transplantes Euclycles of Jesus Zerbini/Hospital Brigadeiro, São Paulo, Brazil
8Hospital Amoral Carvalho, Jaú, Brazil
9Universidade Federal de Minas Gerais, Belo Horizonte, Brazil
10Hospital Israelita Albert Einstein, São Paulo, Brazil
11Hospital do Servidor Público Estadual, São Paulo, Brazil
12Casa de Saúde Santa Marcelina, São Paulo, Brazil
13Universidade Federal de Goiás, Goiânia, Brazil
14Universidade Federal do Ceará, Fortaleza, Brazil
15Instituto de Cancer de São Paulo, São Paulo, Brazil
16Universidade Federal do Paraná, Curitiba, Brazil
17Hospital São Vicente de Paulo, Passo Fundo, Brazil

Correspondence
Matheus Vescovi Gonçalves, R Dr Diogo de Faria 824, CEP 04037-002, São Paulo, SP, Brazil.
Email: Matheus.vescovi@gmail.com

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SUPPORTING INFORMATION
Additional Supporting Information may be found online in the supporting information tab for this article.

Received: 21 March 2017 | Accepted: 5 May 2017

DOI 10.1002/ajh.24785

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.
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 antagonist 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 antagonist 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 antagonist 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 antagonist 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 antagonist 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 antagonist 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 antagonist 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 antagonist 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 antagonist 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 antagonist 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 antagonist 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 antagonist may be considered. It has already been established that both testosterone\(^1\) and estrogens\(^2\) are associated with suppression of serum hepcidin in men.

<table>
<thead>
<tr>
<th>Variables</th>
<th>All patients</th>
<th>Tertiles of urinary prednisolone excretion (pmol/24 h)</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary prednisolone (pmol/24 h)</td>
<td>758 (371–1278)</td>
<td>256 (125–371)</td>
<td>755 (619–904)</td>
<td>1595 (1273–2325)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>51 ± 12</td>
<td>53 ± 12</td>
<td>53 ± 12</td>
<td>49 ± 12</td>
<td>.003</td>
<td></td>
</tr>
<tr>
<td>Male sex (n %)</td>
<td>298 (54)</td>
<td>109 (60)</td>
<td>107 (58)</td>
<td>82 (45)</td>
<td>.006</td>
<td></td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m(^2))</td>
<td>47 ± 16</td>
<td>41 ± 16</td>
<td>46 ± 15</td>
<td>54 ± 13</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Laboratory parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>
<td>5.8 (2.8–11.4)</td>
<td>.003</td>
<td></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>
<td>14.2 ± 1.4</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>EPO (IU/L)</td>
<td>156.0 (80.0–283.0)</td>
<td>189 (102–316)</td>
<td>163 (77–288)</td>
<td>122 (68–233)</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>hs-CRP (mg/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>
<td>16.6 (11.4–22.9)</td>
<td>.28</td>
<td></td>
</tr>
<tr>
<td>Insulin (µU/mL)</td>
<td>11.1 (7.9–16.3)</td>
<td>11.4 (7.8–15.7)</td>
<td>11.2 (8.3–15.1)</td>
<td>10.8 (7.8–15.8)</td>
<td>.53</td>
<td></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.

ACKNOWLEDGMENTS
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST
C.A.J.M.G. received speaking fees and research funding from Vifor Pharma. The other authors have declared that no conflict of interest exists.

Michele F. Eisenga1,2, Robin P. F. Dullaart2, Stefan P. Berger1, Daan J. Touw3, Stephan J. L. Bakker, Carlo A. J. M. Gaillard4
1Department of Nephrology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
2Department of Endocrinology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
3Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Correspondence
M. F. Eisenga, Department of Internal Medicine, Division of Nephrology, University Medical Center Groningen, P.O. Box 30.001, 9700 RB Groningen, The Netherlands.
Email: m.f.eisenga@umcg.nl

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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.1 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.2 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.2,3 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.