Serum hepcidin-25 levels predict the progression of renal anemia in patients with non-dialysis chronic kidney disease

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Abstract

Background. Hepcidin is associated with iron-restricted erythropoiesis. A previous cross-sectional study showed that serum hepcidin-25 levels are negatively associated with the hemoglobin concentration in non-dialysis chronic kidney disease (CKD) patients with sufficient iron stores. This longitudinal study aimed at ascertaining the association between hepcidin-25 levels and the progression of renal anemia.

Methods. We selected 335 non-dialysis CKD patients who showed hemoglobin concentrations >10 g/dL and who were not receiving erythropoiesis-stimulating agent (ESA) therapy, from among the subjects of our previous study, who had been recruited between February and June 2007 in a previous study. The primary outcome was the start of the ESA therapy or hemoglobin concentrations remaining below 10 g/dL for >3 months, by 31 December 2010. The patients were classified into high- and low-ferritin groups depending on their median ferritin levels. The Cox proportional hazard model with restricted cubic spline curve analysis was used to determine the association between hepcidin-25 levels and the outcome for each group.

Results. The hepcidin-25 level was a significant predictor both for the high-ferritin group (P = 0.04, linearity = 0.02) and for the low-ferritin group (P = 0.04, linearity P = 0.02). The spline curve for the high-ferritin group showed that higher hepcidin-25 levels had a high log-relative hazard.

Conclusions. Higher hepcidin-25 levels predict the progression of anemia in non-dialysis CKD patients with sufficient iron stores, indicating the involvement of hepcidin in the progression of anemia in non-dialysis CKD patients.

Keywords: anemia; ferritin; hepcidin-25; non-dialysis CKD

Introduction

Anemia in patients with chronic kidney disease (CKD) is associated with numerous adverse outcomes including cardiovascular disease and mortality, and it has a multifactorial etiology. The pathogenesis could be a result of inflammatory effects and iron-restricted erythropoiesis in addition to erythropoietin (EPO) deficiency. Recombinant human erythropoietin (rhEPO) has brought about a dramatic change in anemia therapy for patients with CKD. However, rhEPO resistance, often associated with iron-restricted erythropoiesis, remains a problem [1].

Hepcidin, a key regulator of systemic iron metabolism [2], is a mediator of anemia of inflammation [3] and is associated with iron-restricted erythropoiesis [4]. Hepcidin is synthesized in the liver as an 84-amino acid prepropeptide and subsequently processed to a 60-amino acid propeptide (prohepcidin). Further enzymatic cleavage of prohepcidin produces the bioactive 25-amino acid hepcidin (hepcidin-25) [5, 6]. The hepcidin level is upregulated by inflammation [7, 8] and increased iron stores and is downregulated by iron depletion [9].

In our previous cross-sectional study [10], the association between hepcidin-25 and anemia in patients with non-dialysis CKD was demonstrated. The association between the serum hepcidin-25 level and the hemoglobin concentration varied according to the level of ferritin. In addition, the serum hepcidin-25 level was negatively associated with the hemoglobin concentration in patients with sufficient iron store. However, the cause-and-effect relationship between hepcidin-25 and renal anemia could not be evaluated from those data because of the cross-sectional study design. To our knowledge, the association between hepcidin-25 levels and the progression of renal anemia has not been previously demonstrated using a longitudinal analysis.
We hypothesized the involvement of hepcidin in the progression of anemia in non-dialysis CKD patients. The present retrospective cohort study was conducted to evaluate the validity of this hypothesis.

Materials and methods

Study population

In this study, we enrolled 335 non-dialysis CKD patients who had hemoglobin concentrations of >10 g/dL and who had not received ESA therapy within the 6-month period before the baseline evaluation in order to evaluate the progression of anemia. The patients were selected from among the 505 ambulatory patients with non-dialysis CKD who participated in a previously published [10] cross-sectional study and who were enrolled in this cross-sectional study between February and June 2007. The enrolled patients had not received renal replacement therapy (RRT) or parenteral iron therapy, and they did not have evidence of active bleeding or active infection at the time of enrollment. Data were collected from the medical charts of these patients retrospectively. The follow-up evaluations were not performed prospectively because the longitudinal study was not planned at the beginning of the previous cross-sectional study.

The protocol was approved by the Institutional Review Board of Osaka General Medical Center, and all patients provided informed consent. The procedures followed were performed in accordance with the Declaration of Helsinki.

Clinical measurements

Data on demographic characteristics and blood samples were collected during enrollment, as previously described [10]. The blood samples were immediately centrifuged, separated into aliquots and stored at −80°C for future assays. The levels of serum hepcidin were quantified using liquid chromatography-tandem mass spectrometry (LC-MS/MS) with a previously reported method [11]. Isotopic human synthetic hepcidin (Peptide Institute, Osaka, Japan) was mixed with each sample as an internal standard. The samples were then introduced into a PLRP-S column (5 mm, 300 Å, 150 × 2.1 mm; Varian, Inc., Palo Alto, CA) and examined using LC-MS/MS in a 4000 QTRAP LC-MS/MS System (Applied Biosystems, Foster City, CA). The concentration of serum hepcidin was expressed in terms of nanograms per milliliter. The intra- and inter-assay coefficients of variation were <6.7 and <8.8%, respectively. The lower limit of detection was 1.0 ng/mL. Interleukin-6 (IL-6) was measured using an enzyme-linked immunosorbent assay (ELISA) kit (Quantikine HS; R&D Systems, Minneapolis, MN) according to the assayed using an enzyme-linked immunosorbent assay (ELISA) kit (Quantikine HS; R&D Systems, Minneapolis, MN) according to the manufacturer’s protocol. Serum EPO concentrations were determined by radioimmunoassay (Mitsubishi Chemical Medience, Tokyo, Japan). Other serum parameters such as serum ferritin levels, serum iron levels and total iron-binding capacity (TIBC) were measured using standard laboratory techniques. Transferrin saturation (TSAT, %) was calculated by dividing the serum iron concentration by the TIBC. The estimated glomerular filtration rate (eGFR) was calculated by using the Modification of Diet in Renal Disease formula, modified for the Japanese: eGFR = 194 × (serum creatinine level) − 1.094 × (age) − 0.287 (×0.793, if female) [12].

Exposure and outcome

The exposure was the hepcidin-25 level measured from the samples at baseline. The primary outcome was defined as the patients whose hemoglobin concentrations remained >10 g/dL for >3 months or those patients starting ESA therapy. ESA therapy was started according to the diagnosis of renal anemia after ruling out other causes of anemia and as per the recommendation of ESA treatment by a nephrologist from the Department of Kidney Disease and Hypertension, Osaka General Medical Center in routine clinical practice. The nephrologists were blinded to the serum hepcidin-25 levels of the patients. Patients were censored upon loss to follow-up, death, initiation of RRT or at the end of the observation period (31 December 2010).

Statistical analyses

Baseline characteristics were assessed using standard descriptive statistics. In the previous cross-sectional study, all patients had been stratified into two groups on the basis of their median ferritin levels (91 ng/mL); this stratification was maintained in this study. For sensitivity analysis, the patients were also stratified at a ferritin level of 100 ng/mL, which is the minimum ferritin level recommended by the 2006 National Kidney Foundation Disease Outcomes Quality Initiative [13] for non-dialysis CKD patients on ESAs.

Time-to-event analyses were used to examine the risks of the outcome according to the baseline hepcidin-25 levels, which were expressed as the continuous variables. For the univariate analysis, Kaplan–Meier methods, log-rank testing for categorical variables and the unadjusted Cox proportional hazards model with a restricted cubic spline curve analysis for continuous variables were used. A restricted cubic splines graph with 3 degrees of freedom was used to illustrate the relationship between hepcidin-25 levels, as a continuous variable, and the outcome. This was also used to examine non-linear associations as continuous predictors, instead of using potentially inappropriate assumptions concerning linearity. For the multivariate analysis, the Cox proportional hazards model was used with a restricted cubic spline curve analysis, after adjusting for the relevant covariates. The covariates were selected by the forced-entry and stepwise methods; age and sex were selected by the forced-entry method and other covariates were selected by the stepwise method. Schoenfeld residuals were used to confirm the proportionality assumption. All results were based on the analysis of the available data, without any imputation procedure. P values of <0.05 were considered statistically significant. All analyses were performed using the R statistical software (R Foundation for Statistical Computing, version 2.11.1; R Development Core Team) and JMP 8 (SAS Institute).

Results

The baseline characteristics are summarized in Table 1 for the all-patient, high-ferritin and low-ferritin groups. The mean (SD) eGFR and age at the baseline were 48.8 mL/min per 1.73 m² (24.4 mL/min per 1.73 m²) and 61.4 years (15.0 years), respectively. Patients from the high-ferritin group were male dominant and had significantly lower eGFR and EPO levels and significantly higher TSAT and hepcidin-25 and IL-6 levels than those from the low-ferritin group.

During a median follow-up period of 3.6 years, 66 patients achieved the outcome: 33 from the high-ferritin group and 33 from the low-ferritin group. The ESA therapy was started for 52 of these patients. The number of patients who achieved the outcome is shown Figure 1. The mean hemoglobin concentration of the 52 patients at the start of the ESA therapy was 9.7 g/dL (0.9 g/dL). During the follow-up period, RRT was started for three patients: two from the high-ferritin group and one from the low-ferritin group. Oral iron supplementation was started for nine patients: two patients from the high-ferritin group and seven from the low-ferritin group. Parenteral iron supplementation was not initiated until ESA therapy was started.

The associations between the outcome and the covariates in the univariate analysis are presented in Table 2. In the univariate analysis for the all-patient group, age, eGFR and levels of hemoglobin, IL-6 and TSAT were found to be significantly associated with the outcome. In the high-ferritin group, age, eGFR and levels of hemoglobin and IL-6 were found to be significantly associated with the outcome. In the low-ferritin group, age, eGFR, levels of hemoglobin, EPO, IL-6 and hepcidin-25 and TSAT were significantly associated with the outcome.

Multivariate analyses were performed using the cubic spline models of the Cox proportional regression analysis
for the all-patient group (Figure 2). For this group, eGFR and the hemoglobin and hepcidin-25 levels were selected as covariates using the stepwise method. The cubic spline models, adjusted for age, sex, eGFR and levels of hemoglobin and hepcidin-25, showed that the hepcidin-25 level was not a significant predictor of the progression of renal anemia in the all-patient group (P = 0.3, linearity P = 0.2). These analyses were also performed after adjusting for age, sex, eGFR, levels of hemoglobin and ferritin, and TSA T. Neither the ferritin level (P = 0.8, linearity P = 0.9) nor the TSA T (P = 0.4, linearity P = 0.3) was significant predictors of the outcome in this group.

The association between hepcidin-25 levels and the progression of renal anemia was also examined using the cubic spline models of the multivariate Cox proportional regression analysis for the high- and the low-ferritin groups (Figure 3). The eGFR and hemoglobin and hepcidin-25 levels were selected as covariates for the high-ferritin group, using the stepwise method. The cubic spline models of the Cox proportional regression analysis, adjusted for age, sex, eGFR and levels of hemoglobin and hepcidin-25, showed that the hepcidin-25 level was a significant predictor of the outcome in this case (P = 0.04, linearity P = 0.02). Even when the IL-6 level was added into the model, the association between the hepcidin-25 level and the outcome remained significant (P = 0.04, linearity P = 0.02). Similarly, for the low-ferritin group, the eGFR and hemoglobin and hepcidin-25 levels were selected as covariates by using the stepwise method. The similarly adjusted cubic spline models of the Cox proportional regression analysis
showed that the hepcidin-25 level was also a significant predictor in this case (P = 0.04, linearity P = 0.02). When the TSAT was included in the model, instead of the hepcidin-25 level, it was not a significant predictor for either ferritin groups.

Sensitivity analysis

The primary outcome was achieved in 32 of 146 patients whose ferritin levels exceeded 100 ng/mL. The cubic spline curve analysis showed that the hepcidin-25 levels were significantly associated with the outcome (P = 0.04, linearity P = 0.02), while neither the ferritin level (P = 0.5) nor the TSAT (P = 0.4) was associated with the outcome in the patients whose ferritin level was >100 mg/mL (Figure 4).

The association between the hepcidin-25 level and the outcome did not alter when the patients were divided depending on whether their serum ferritin level was 100 ng/mL.

Table 2. Associations between baseline risk factors and the primary outcome using univariate analyses

<table>
<thead>
<tr>
<th>Variable</th>
<th>All-patient group (n = 335)</th>
<th>High-ferritin group (n = 155)</th>
<th>Low-ferritin group (n = 180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (/10 years)</td>
<td>P &lt;0.001 Linearity P 0.06</td>
<td>P 0.09 Linearity P 0.2</td>
<td>&lt;0.001 Linearity P 0.09</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>0.08</td>
<td>0.02</td>
<td>0.4</td>
</tr>
<tr>
<td>eGFR (mL/min per 1.73 m²)</td>
<td>&lt;0.001 Linearity P 0.001</td>
<td>&lt;0.001 Linearity P 0.6</td>
<td>&lt;0.001 Linearity P 0.008</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>&lt;0.001 Linearity P 0.001</td>
<td>&lt;0.001 Linearity P 0.002</td>
<td>&lt;0.001 Linearity P 0.5</td>
</tr>
<tr>
<td>EPO (mIU/mL)</td>
<td>0.7 0.5</td>
<td>0.9 0.8</td>
<td>0.04 0.7</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>&lt;0.001 Linearity P 0.001</td>
<td>0.005 Linearity P 0.01</td>
<td>0.02 0.08</td>
</tr>
<tr>
<td>Ferritin (ng/mL)</td>
<td>0.4 1.0</td>
<td>0.9 0.8</td>
<td>0.005 0.5</td>
</tr>
<tr>
<td>TSAT (%)</td>
<td>0.02 0.3</td>
<td>0.9 0.8</td>
<td>0.002 0.001</td>
</tr>
<tr>
<td>Hepcidin-25 (ng/mL)</td>
<td>0.1 0.07</td>
<td>0.3 0.2</td>
<td>0.002 0.001</td>
</tr>
</tbody>
</table>

eGFR, estimated glomerular filtration rate; EPO, erythropoietin; TSAT, transferrin saturation index.

Fig. 2. Adjusted restricted cubic spline parameters of iron metabolism for the all-patient group. The spline models have 3 degrees of freedom. The multivariate models included age, sex, eGFR and hemoglobin concentration. (a) The serum hepcidin-25 levels were not significantly associated with the outcome (P = 0.3). (b and c) Neither the serum ferritin level (P = 0.8) nor the TSAT (P = 0.4) was associated with the outcome. TSAT, transferrin saturation index; eGFR, estimated glomerular filtration rate.
Discussion

To the best of our knowledge, this is the first direct evidence of the involvement of hepcidin in the progression of anemia in non-dialysis CKD patients. In this longitudinal study, we found that higher serum hepcidin-25 levels predicted the progression of anemia in non-dialysis CKD patients with sufficient iron stores.

The present results demonstrated an association between the serum hepcidin level and the achievement of the primary outcome in the high-ferritin group. The spline curve analysis for the high-ferritin group showed that high hepcidin levels were associated with the progression of renal anemia. There are several reasons why high hepcidin levels could lead to the progression of anemia in non-dialysis CKD patients with sufficient iron stores. First, hepcidin limits iron absorption from the intestine and release from macrophages by controlling the synthesis and activity of several iron transport proteins [14]. This role in iron absorption is consistent with the finding that a chronic excess of hepcidin causes iron-restricted anemia [15]. Secondly, the causal role of hepcidin in the process of anemia of inflammation has been supported by several observations [16]. Recently, IL-6 was reported to play an essential role in the induction of hepcidin in multicentric Castleman disease [17]. Moreover, IL-6-induced hepcidin-25 was reported to be an important modulator of anemia in septic patients with systemic inflammation. CKD is a chronic inflammatory disorder and even CKD patients without significant inflammation showed elevated hepcidin levels. Hence, it is plausible that hepcidin plays a crucial role in the pathogenesis of renal anemia of inflammation [16].

This report suggests that hepcidin could be a useful predictor of the progression of renal anemia. In our earlier cross-sectional study [10], an interaction was found between the serum hepcidin-25 level and the serum ferritin level. In the low-ferritin group, the serum hepcidin-25 level was also a significant predictor of the progression of anemia. However, in contrast to the high-ferritin group, the spline curve for the low-ferritin group showed that the low hepcidin levels were associated with the progression of anemia. This finding supports the result of our cross-sectional study, which showed that hepcidin was positively associated with the hemoglobin concentration in non-CKD patients with normal-to-subnormal iron stores. The low hepcidin level may possibly reflect the absolute iron deficiency and lead to the progression of anemia.

Our study has a few limitations. First, a longitudinal evaluation was not planned at the beginning of the cross-sectional study. Accordingly, we could not thoroughly and prospectively follow-up the subjects. We cannot deny the possibility of a misclassification of the cause of established anemia, since it was based on retrospective medical chart reviews. To minimize the possibility of misclassification, we defined the primary outcome to reflect the progression of renal anemia at the start of ESA therapy and
the hemoglobin concentration remaining <10 g/dL for >3 months. Secondly, the hemoglobin concentrations at the start of ESA therapy may have been different, depending on the nephrologist reviewing the case. Although the ideal hemoglobin concentrations for patients with non-dialysis CKD are not yet well established, the mean hemoglobin concentration of the patients at the start of ESA therapy was 9.7 g/dL (0.9 g/dL). This level occurred at the same time when the patient’s hemoglobin concentration became <10 g/dL. Thirdly, we measured the hepcidin-25 levels only once. A large diurnal variability in serum hepcidin levels has been reported previously [18, 19]. In chronic hemodialysis patients on ESA therapy, hepcidin levels were not predictive of iron needs because hepcidin levels showed intra-individual variability [20, 21]. However, in non-dialysis CKD patients, hepcidin may afford more diagnostic value, as values are lower and may be more stable [22]. In this study, we included only non-dialysis CKD patients not on ESA therapy treatment. Although we found a significant association between higher hepcidin-25 levels and the progression of anemia, the predictive value of one-point measurements of hepcidin in these clinical settings needs to be further investigated. Fourthly, we did not measure urinary hepcidin excretion and the levels of hepcidin isoforms such as hepcidin-20 and hepcidin-22. Therefore, we could not obtain any information on the association between these parameters and renal anemia. Fifthly, as in any observational study, we could not account for unmeasured or residual confounding factors.

In conclusion, we found in this longitudinal study that higher serum hepcidin-25 levels predicted the progression of anemia in non-dialysis CKD patients with sufficient iron stores. Our results indicate the involvement of hepcidin in the progression of anemia in non-dialysis CKD patients. These findings imply that targeting the hepcidin-ferroportin axis may enable the development of therapeutic strategies to retard the progression of anemia in non-dialysis CKD patients.

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Conflict of interest statement. None declared.

References

BLOG COMMENTARY

Serum hepcidin-25 levels predict the progression of renal anemia in patients with non-dialysis chronic kidney disease

NDTERA-EDTA OLA has selected this publication for comments by its faculty in view of its quality and potential educational value. Find out more on www.gkaonlineacademy.com/ndt.

Niihata and colleagues from Japan report the association between high serum hepcidin25 levels and the progression of anemia in patients with CKD (eGFR around 48ml/min). High hepcidin levels predicted anemia progression to Hb levels <10g/dl in patients described as having high or low iron stores based on a serum ferritin cut off level of 91ng/ml.

A quick reminder of iron metabolism is warranted to appreciate the key role of hepcidin in its metabolism and availability. Oral iron is absorbed through the duodenum and circulates bound to transferrin to be delivered to the bone marrow for erythropoiesis. Also the pool of circulating iron is supplied by the breakdown of ageing erythrocytes phagocytosed by reticuloendothelial macrophages that recycle iron back into the circulation. Iron storage also takes place in hepatocytes. On average, approximately 1 to 2mg of iron is provided daily through intestinal absorption, thus balancing losses. As approximately 20mg/day of iron is required for erythropoiesis, this is largely provided from iron recycled from macrophages and hepatic stores. Hepcidin, through its binding and degradation of ferroportin, an iron channel on the surface of enterocytes, macrophages, and hepatocytes, inhibits iron mobilization from its stores into the circulation (1).

In the ageing general population, strong correlations have been observed between plasma hepcidin levels and body iron status, C-reactive protein as well as erythropoietin levels. Significantly higher hepcidin levels were found in patients with anemia and CKD (2). It makes therefore good sense that high circulating levels of hepcidin25 may predict subsequent progression of anemia in CKD.

The NDTERA-EDTA OLA readers may be interested to learn more from the authors of this very interesting article about:

(1) In their study, the relationship between hepcidin25 levels and iron status/stores is largely defined by a serum ferritin level above (high stores) or below (low stores) 91ng/ml. This cut off point may not be representative of true iron stores status in CKD 3 and 4 patients where a higher cut off of around 500ng/ml, as stipulated by KDIGO 2012, may be more appropriate (3).

(2) Could the progression of anemia reflect the progression of CKD in this population with the rise in serum hepcidin25 levels mirroring the fall in Hb and that of eGFR with time? In that respect, it would be informative to know whether patients with high serum hepcidin25 and falling Hb also have a falling eGFR. Changes in the three parameters with time may underlie the relationship between high, or may be rising, hepcidin and progressive anemia.

(3) Whether a serum Heparin25 : Ferritin ratio or Hepcidin25 : TSAT ratio may be more informative and predictive that the circulating hepcidin25 level alone. Such a ratio would adjust for iron stores variability and correct to some extent for the interdependency of serum hepcidin levels and iron stores.
Targeting the hepcidin-ferroportin axis may open the way to new interventions for the management of anemia of CKD (4).

References


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Abstract

Background. The role of vitamin D in kidney stone disease is controversial. Current evidence is inconsistent and existing studies are limited by small sample populations.

Methods. We used the third National Health and Nutrition Examination Survey (NHANES III), a large US population-based cross-sectional study, to determine the independent association between serum 25-hydroxyvitamin D [25(OH)D] concentration and prevalent kidney stone disease in a sample of 16 286 men and women aged 18 years or older. A prevalent kidney stone was defined as self-report of any previous episode of kidney stones.

Results. Among 16 286 adult participants, 759 subjects reported a history of previous kidney stones. Concentrations of serum 25(OH)D were not different between stone formers and non-stone formers (mean 29.28 versus 29.55 ng/mL, P = 0.57). Higher 25(OH)D concentration was not associated with increased odds ratio (OR) for previous kidney stones [OR = 0.99, 95% confidence interval (CI) 0.99–1.01] after adjustment for age, sex, race, history of hypertension, diabetes, body mass index, diuretic use and serum calcium. Furthermore, after we divided 25(OH)D concentrations into quartiles, or into groups using clinically significant cut-offs (e.g. 40 and 50 ng/mL), still no significant differences were found in stone formation in group comparisons.

Conclusions. High serum 25(OH)D concentrations are not associated with prevalent kidney stone disease in NHANES III participants. Prospective studies are needed to clarify the relationship between vitamin D and kidney stone formation, and whether nutritional vitamin D supplementation will increase risk of stone recurrence.

Keywords: 25-hydroxyvitamin D; kidney stone disease; Third National Health and Nutrition Examination Survey

Introduction

Kidney stone disease is common in the general population with an estimated prevalence of around 10–15% in males and 3–5% in females [1]. The calcium-based kidney stone is the most common type (>80%), and high urine calcium excretion is a strong risk factor for stone formation [1, 2]. Prior studies have shown that a higher concentration of the active vitamin D metabolite, 1,25-dihydroxyvitamin D [1,25(OH)2D], is associated with increased urinary calcium excretion [3, 4], which can lead to increased risk of stone formation.

However, less is known about the relationship between 25-hydroxyvitamin D [25(OH)D] concentrations and kidney stones. Existing studies among stone formers have failed to show a correlation between serum 25(OH)D and 1,25(OH)2D concentrations [5, 6]. In a small study involving 160 stone formers and 217 controls, Netelenbos et al. [7] failed to show any significant difference in serum 25-