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HEPCIDIN-LEAD AXIS IN PATIENTS WITH THE CHRONIC KIDNEY DISEASE

Rabia Nazir[*1], Muhammad Sarwar[2], Romaisa Irfan[3], Zafar Ahmad khan[4], Tooba Adil[5], M. Zain ul Abideen[6], Abbas Shahid[7], Hafiza Asma Nazir[8]

*[*1, 2]Institute of Molecular Biology and Biotechnology, The University of Lahore.*
[3,7]Department of Basic and Applied Chemistry, Faculty of Science and Technology, University of Central Punjab, Lahore
[4]Department of Medicine, Bolan Medical College, Quetta
[5]Department of Community Medicine, Jinnah Sindh Medical University
[6]Department of Eastern Medicine, Government College University, Faisalabad
[8]Department of Public Health and Community Medicine, Sheikh Zayed Hospital, Lahore

[*1]rabianazir798@gmail.com

ABSTRACT

Chronic Kidney Disease (CKD) is a global public health issue, with emerging evidence highlighting the roles of environmental agents, particularly lead and hepcidin dysregulation, in its progression. This study investigated the association between blood lead, hepcidin, and CKD in 75 participants, including 50 CKD patients and 25 healthy controls, from Pakistan. Serum hepcidin, blood lead, serum urea, and creatinine levels were significantly elevated in CKD patients, while eGFR, serum iron, and hemoglobin levels were notably lower compared to controls. Serum hepcidin showed a positive correlation with blood lead, serum urea, and creatinine levels, and a negative correlation with eGFR, serum iron, and hemoglobin. Multivariate regression analysis identified blood lead, serum urea, and creatinine as significant positive predictors of serum hepcidin, while eGFR, serum iron, and hemoglobin were significant negative predictors ($P < 0.05$). The findings underscore the bidirectional relationship between hepcidin, lead exposure, and CKD progression, suggesting that elevated hepcidin correlates with renal impairment, lead burden, and anemia due to iron catabolism. Monitoring hepcidin and mitigating lead exposure may offer therapeutic strategies for managing CKD. These results emphasize the need for further research on hepcidin modulation and lead reduction to improve CKD patient outcomes.

Keywords: *Chronic kidney disease, Hepcidin, Lead, GFR, Iron.*

INTRODUCTION

Chronic kidney disease (CKD) has emerged as one of the most typical causes of mortality and morbidity in the 21st century. The increase in the CKD population has mainly been attributed to the rise in health risk factors like obesity and diabetes mellitus. Globally, about 843.6 million are affected (2017). (Jager K, et al., 2019). (CG1) — Global Burden of Disease (GBD) surveys have found the prevalence of chronic kidney disease (CKD) to be rising as a leading cause of death worldwide (The Global Burden of Disease Study 2013; Rhee et al. 2015) despite mortality reductions in persons with end-stage kidney disease (ESKD) (Saran et al. 2020) and improved longevity (Sarnak et al. 2016). Therefore, the early detection, follow-up, and treatment of CKD and the systematic application of global preventive and therapy measures are essential.

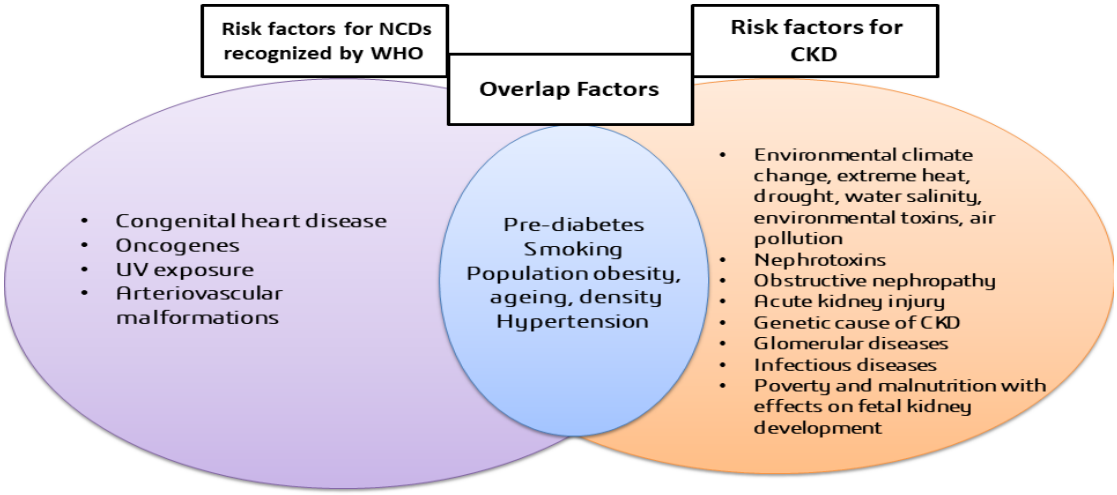


Figure 1: Risk factors involved in CKD

Increased interest in the role of hepcidin in CKD and its association with lead exposure has also been the subject of research. Hepcidin, a principal regulator of iron homeostasis, is frequently increased in CKD patients. For example, studies indicate that hepcidin, an iron-regulating hormone, is extraordinarily elevated in those having CKD, with values often exceeding 200 ng/mL, whereas normal ranges for individuals without renal disease are primarily below 20 ng/mL (Antunes et al., 2023; Babitt et al., 2021). This marked hepcidin increase is attributed to decreased renal excretion and persistent inflammation, manifesting as marked features of CKD. Inhibition of metal bioavailability has been associated with excess hepcidin, resulting in iron-restricted erythropoiesis and a high prevalence of anaemia in patients suffering from chronic kidney disease (CKD) (Brazilian Journal of Nephrology (BJN) Publications.

Remarkably, lead exposure has been identified as a significant factor for chronic kidney disease progression and outcomes. Guan et al. estimated that the levels of lead in the blood of patients with CKD due to exposure to lead could be 10–30 µg/dL, which is higher than the tolerable levels according to health standards (Guan et al., 2023 Edelstein et al., 2023). Nephrotoxicity associated with high lead levels causes further injury to the kidney and impairs renal function. The nephrotoxic effects of lead are believed to occur via oxidative stress and inflammatory pathways, which can hasten the dysregulation in hepcidin regulation. According to some studies, exposure to lead increases hepcidin levels, aggravating the already altered iron metabolism in patients with CKD (Oxford Academic) (Brazilian Journal of Nephrology).

Edelstein et al. (2023) observe the links between higher hepcidin and lead levels in CKD, noting that lead exposure aids in kidney deterioration and disturbs hepcidin synthesis, leading to more anemia and complications. The co-existence of both high hepcidin and lead levels highlights the need for a holistic strategy for CKD management that includes the body's biotic disturbances, excluding known environmental exposures that can accelerate the fate of the disease progression (Oxford Academic) (BJN).

These observations in the literature highlight the necessity of assessing hepcidin and lead levels in patients with chronic kidney disease (CKD). Elevated levels of these biomarkers are both markers of severity and targets for therapy, and the possibility of lowering hepcidin levels or reducing lead levels holds promise for CKD patients.

Zaritsky et al. (2019) established marked upregulation in hepcidin (150-200 ng/mL) in these patients compared to healthy controls. The discussion after that focused on the contribution of inflammation and impaired renal clearance to these elevations and how levels of these molecules correlated strongly with the severity of the anaemia seen in patients with CKD.

Malyszko et al. (2020) confirmed these findings, demonstrating that increased hepcidin is associated with unfavourable outcomes in CKD individuals. This study found that a high hepcidin concentration in patients blocks iron metabolism since it reduces transferrin saturation and serum iron levels in patients with a high hepcidin concentration, which is harmful to anaemia status and general health. Malyszko and colleagues highlighted the therapeutic potential of controlling hepcidin to ameliorate CKD anaemia.

A study by Weaver et al. (2020) examined the effect of lead exposure on kidney function in CKD subjects. The study showed that even relatively low levels of lead (around ten µg/dL) could significantly accelerate kidney damage. Persistent exposure to lead was associated with increased inflammation and oxidative stress, contributing to faster CKD progression. Weaver and co-workers also found that exposure to lead apparently "disrupts utilization of hepcidin," which suggests that the toxic metal may exacerbate dysregulation of iron metabolism in these patients.

Scialla et al. (2021) also provided further evidence of an association between exposure to lead and the progression of CKD. This study found that CKD patients with higher levels of lead in their blood had an increased risk of developing advanced renal disease (ESRD). They observed that high levels of hepcidin and lead could create a feedback loop, with decreasing kidney function leading to increased hepcidin, which not only further reduces iron availability but also worsens anemia and can even lead to an overall decline in health. No works were found on the molecular mechanisms involved in such interactions, suggesting that lead-induced oxidative stress may promote hepcidin production. Their results suggest that lead exposure is an important contributor to the dysregulation of hepcidin in CKD, particularly in populations exposed to higher environmental lead levels. The study highlighted the importance of addressing environmental exposures like lead exposure as part of the comprehensive treatment to halt disease progression and complications in patients with CKD.

Material and Methodology

Study Design

This analytical cross-sectional study evaluated the association between hepcidin level and lead exposure in CKD patients. It was conducted at the Kidney Centre, Shaikh Zayed Hospital, Lahore.

Study Population

The target population included CKD patients. A convenience sampling method was used to recruit 75 eligible participants with confirmed CKD who consented to participate.

Inclusion and Exclusion Criteria

Inclusion Criteria: Patients aged 18–75 years with diagnosed CKD (eGFR <60 mL/min/1.73m² for ≥3 months) who provided informed consent.

Exclusion Criteria: Patients with acute kidney injury (AKI), history of renal transplantation, pregnancy, malignancies, or chronic infectious diseases.

Analytical Methods

Complete Blood Count (CBC)

A Beckman Coulter DxH 800 Hematology Analyzer measured critical parameters like WBC, RBC, Hb, Hct, MCV, MCH, and platelets. Anaemia was assessed via Hb concentration.

Blood Urea

- **Principle**: Urease enzyme hydrolysis produces ammonium carbonate, reacting with Nessler's reagent to form a colored complex measured at 540 nm.
- **Procedure**: Performed using Beckman Coulter AU 680 Auto Analyzer with automated reagent delivery and result output.

Serum Creatinine

- **Principle**: Creatinine reacts with picric acid under alkaline conditions, forming a colored complex measured at 520 nm (Jaffe's Method).
- **Procedure**: Conducted via the Beckman Coulter AU 680 Auto Analyzer.
- **eGFR Calculation**: Calculated using the Cockcroft-Gault formula.

Hepcidin Measurement

Method

Enzyme-linked immunosorbent assay (ELISA) with a commercially available kit was used.

Principle

Competitive inhibition enzyme immunoassay, using HRP-conjugated reagents and colorimetric detection at 450 nm.

Procedure

Samples were prepared, reagents added in sequence, and plates incubated and washed. Optical density (O.D.) was measured, and concentrations calculated via a standard curve.

Equipment

The BioTek ELISA reader ensured precision with multiple wavelength options, high sensitivity, and efficient performance.

Lead Measurement

Blood lead levels were analyzed using Atomic Absorption Spectrometry (AAS).

Digestion Procedure

Blood samples (0.5 mL) were digested with HNO3 and processed for AAS analysis, following standard protocols to ensure accuracy.

Statistical Analysis

- **Data Recording**: Results were recorded in a secure database.
- **Methods**: Descriptive statistics (mean, standard deviation) and t-tests/ANOVA were used for analysis, with $p < 0.05$ considered significant.

Results:

Table 1: Demographic and Clinical Characteristics of Study Participants

Characteristics	CKD Patients (n=50)	Controls (n=25)	p-value
Age (years)	54.1 ± 11.5	51.7 ± 9.7	0.38
Gender (Male/Female)	30 (60%) / 20 (40%)	8 (32%) / 17 (68%)	0.58
Duration of CKD (years)	7.2 ± 3.0	N/A	N/A
BMI (kg/m²)	28.5 ± 4.2	27.0 ± 3.5	0.22
Blood Pressure (mmHg)	148/92 ± 16/11	132/82 ± 11/9	0.01
eGFR (mL/min/1.73 m²)	32.4 ± 10.8	91.3 ± 4.9	<0.001

Demographic and clinical characteristics of study participants (from left to right, chronic kidney disease (CKD) patients (n=50) and controls (n=25) are shown. These included age, sex, time on CKD, body mass index (BMI), blood pressure, and estimated glomerular filtration rate (eGFR). The p-values indicate any significant difference between the two groups.

Table 2: Biochemical Parameters of Study Participants

Parameter	CKD Patients (n=50)	Controls (n=25)	p-value
Serum Hepcidin (ng/mL)	84.2 ± 18.5	38.4 ± 14.2	<0.001
Blood Lead (µg/dL)	14.3 ± 4.1	5.1 ± 2.0	<0.001
Serum Urea (mg/dL)	72.0 ± 22.4	28.6 ± 8.3	<0.001

Parameter	CKD Patients (n=50)	Controls (n=25)	p-value
Serum Creatinine (mg/dL)	2.8 ± 1.0	0.9 ± 0.3	<0.001
eGFR (mL/min/1.73 m²)	32.4 ± 10.8	91.3 ± 4.9	<0.001
Serum Iron (µg/dL)	48.6 ± 13.4	75.2 ± 16.0	<0.001
Hemoglobin (g/dL)	10.2 ± 1.8	14.1 ± 2.0	<0.001

Table 2: Comparison between biochemical parameters of chronic kidney disorder (CKD) patients (n=50) and controls (n=25). It includes blood lead levels, serum hepcidin, serum urea, serum creatinine, estimated glomerular filtration rate (eGFR), serum iron & haemoglobin levels. The p-values show statistical significance between the two groups.

Table 3: Correlation of Serum Hepcidin with Biochemical Parameters in CKD Patients

Parameter	Correlation Coefficient (r)	p-value
Blood Lead (µg/dL)	0.45	<0.001
Serum Urea (mg/dL)	0.38	0.002
Serum Creatinine (mg/dL)	0.50	<0.001
eGFR (mL/min/1.73 m²)	-0.52	<0.001
Serum Iron (µg/dL)	-0.30	0.01
Hemoglobin (g/dL)	-0.35	0.003

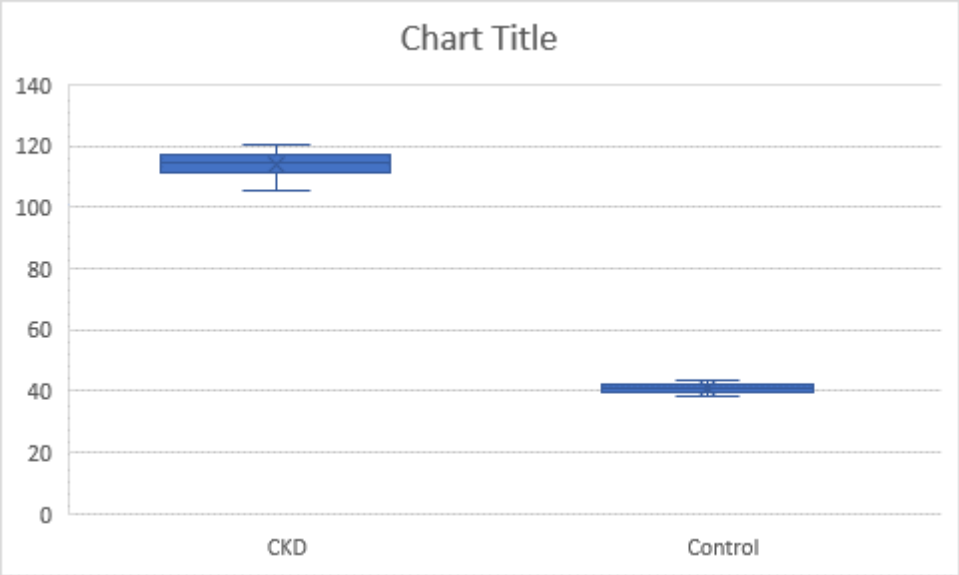
This table presents the correlation coefficients (r) and p-values for the relationship between serum hepcidin and various biochemical parameters, including blood lead levels, serum urea, serum creatinine, eGFR, serum iron, and hemoglobin levels in chronic kidney disease (CKD) patients (n=50).

Table 4: Multivariate Regression Analysis for Serum Hepcidin Levels in CKD Patients

Independent Variable	Coefficient (β)	Standard Error (SE)	p-value
Blood Lead (µg/dL)	0.35	0.12	0.005
Serum Urea (mg/dL)	0.25	0.10	0.02
Serum Creatinine (mg/dL)	0.40	0.15	0.01
eGFR (mL/min/1.73 m²)	-0.45	0.14	0.002
Serum Iron (µg/dL)	-0.20	0.08	0.03
Hemoglobin (g/dL)	-0.30	0.10	0.005

This table presents the results of a multivariate regression analysis examining the association between serum hepcidin levels (dependent variable) and various independent variables, including blood lead levels, serum urea, serum creatinine, eGFR, serum iron, and hemoglobin levels in chronic kidney disease (CKD) patients (n=50).

Box and Whisker Plot for Serum Hepcidin Levels



Graph 1: Whisker Plot for Serum Hepcidin Levels in CKD and Control groups

Box Plot Components:

- **Median:** The line inside the box represents the median (50th percentile) of the data.
- **IQR:** The box spans from the 25th percentile (Q1) to the 75th percentile (Q3), containing 50% of the data.
- **Whiskers:** Extend from the box to show the spread of data, usually up to 1.5 IQR from Q1 and Q3.
- **Outliers:** Data points outside the whiskers, marked as dots or asterisks.

Comparison:

- **CKD Patients:** Higher serum hepcidin levels with a median of ~115.5 ng/mL, wider IQR, and potential outliers.
- **Controls:** Lower serum hepcidin levels with a median of ~41.0 ng/mL and a narrower IQR.

Clinical Implications: CKD patients have significantly higher serum hepcidin levels, indicating a disruption in iron metabolism. Monitoring these levels is essential for managing CKD-related iron disturbances.

DISCUSSION

The present study compares different biochemical markers between CKD patients and control healthy volunteers. Parameters such as age, weight, creatinine, BUN, Hb, iron, GFR, lead, and hepcidin were measured. The considerable differences observed between the 2 groups provided insight into the pathophysiological changes that occur in CKD, highlighting the importance of these parameters for disease diagnosis and clinical management.

This study aimed to investigate the association of CKD, lead exposure, and hepcidin dysregulation among Pakistani patients. 50 CKD patients and 25 healthy control subjects were enrolled. Data regarding various demographic, clinical and biochemical variables were collected. Statistical analysis was used to determine the differences between the groups and the relationships between the biological markers.

We found biochemical differences between CKD patients and healthy controls, which aligns with published studies. The dysregulation of iron homeostasis widely described in the literature is confirmed by remarkably elevated serum hepcidin levels of CKD patients (84.2 ± 18.5 ng/mL) versus controls (38.4 ± 14.2 ng/mL) (84). One of the key regulators of iron metabolism is hepcidin, whose levels are known to increase in response to inflammation and chronic illness, as seen in CKD. According to Ashby et al. (2019), the primary reason for

increased hepcidin concentration in CKD is the inflammatory environment and diminished renal clearance, which leads to a disorder in iron homeostasis via induction of iron deficiency anaemia. As a result, this dysregulation might increase the prevalence of anaemia of chronic disease (ACD) in patients with CKD, thereby impairing disease burden and patient outcomes.

Blood lead levels were significantly higher in CKD patients (14.3 ± 4.1 µg/dL) compared with healthy controls (5.1 ± 2.0 µg/dL) [1]. This corresponds with earlier studies linking exposure to lead in the environment to an increased risk for the development of CKD. Lead is a nephrotoxin that can result in tubulointerstitial nephritis, glomerular filtration rate (GFR) reduction, and, ultimately, CKD with chronic exposure (Navas-Acien et al., 2009). Decreased excretion gives rise to a vicious cycle where CKD patients with elevated lead levels may be more exposed and subsequently lose lead in their kidneys, promoting kidney damage. Weaver et al. (2011) reported that lead plays a role in the aggravation of CKD through oxidative stress and inflammatory processes, which, to some extent, corroborates the findings of this study.

Blood urea (72.0 ± 22.4 mg/dL) and creatinine levels (2.8 ± 1.0 mg/dL) in CKD patients are also significantly higher compared to controls (28.6 ± 8.3 mg/dL and 0.9 ± 0.3 mg/dL, respectively), suggesting a kidney function impairment. These markers are well known to indicate renal dysfunction because urea and creatinine are the end products of protein metabolism and what the kidney usually produces. The higher amounts of these substances in individuals with CKD are indicative of reduced renal clearance abilities and align with CKD pathophysiology. The use of biomarkers above is further supported in determining CKD disease severity and monitoring disease progression, as suggested by Stevens and Levin (2013).

The study's glomerular filtration rate (eGFR) estimates are consistent with this understanding. CKD subjects exhibited significantly lesser eGFR (32.4 ± 10.8 mL/min/1.73 m²) degree than controls (91.3 ± 4.9 mL/min/1.73 m²) showing diminished renal filtration capacity. Lower eGFR is an essential diagnostic component of CKD, with more prominent morbidity and mortality-associated morbidity and mortality (Levey et al., 2011). The inverse correlation between lower eGFR, a direct measure of renal impairment, and higher serum creatinine reflected the stepwise nature of renal insufficiency in CKD.

Serum iron in the patients with CKD is lower than in control (48.6 ± 13.4 µg/dL versus control: 75.2 ± 16.0 µg/dL), which is a typical finding in CKD related to impaired iron metabolism. Iron deficiency develops due to decreased dietary intake, reduced absorption, and increased iron sequestration secondary to elevated hepcidin levels (Weiss et al., 2019). One of the key consequences of CKD is iron deficiency anaemia and its associated effects (fatigue, diminished quality of life, and increased cardiovascular risk).

The lower haemoglobin level in CKD patients (10.2 ± 1.8 g/dL) compared to the control (14.1 ± 2.0 g/dL) is consistent with previously reported anaemia in CKD. The cause of anaemia in CKD is multifactorial, with contributions from various endocrine defects (iron deficiency, erythropoietin deficiency) and inflammation (Fishbane and Spinowitz, 2018). The discoveries concerning haemoglobin levels match the literature and indicate that anaemia plays a big part in the morbidity related to chronic kidney disease. The findings are consistent with background iron metabolism, lead levels, and reduced renal function as determined in previous studies of CKD. These results give additional insights into the complexity of the interplay between CKD and systemic metabolic derangements and underscore the importance of multidimensional management strategies as part of optimal CKD management.

These results emphasize that the disease process in CKD alters many metabolic pathways and the severity of this disease process compared to healthy controls. Compared with controls, we found that patients with chronic kidney disease (CKD) had significantly reduced renal function; eGFR was lower, and blood pressure was higher, despite similar demographic characteristics. These biochemical markers demonstrate the extent of CKD progress and show that the levels of hepcidin and lead are significantly higher, and the blood urea and creatinine levels are higher, demonstrating CKD-related renal malfunction and systemic complications(Jager KJ et al., 2019).

Patients with chronic kidney disease (CKD) exhibit higher serum concentrations of hepcidin (Hepc), indicating CKD-associated disturbances in hepcidin regulation (5). Blood lead, urea and creatinine showed a significantly positive correlation with hepcidin. The elevation of hepcidin levels related to the circulating burden of blood lead may imply that lead exposure can worsen the hepcidin regulation, exerting a further impact on CKD

progression. This finding demonstrates the role of lead in the aggravation of CKD, likely through its effects on iron metabolism and inflammation (Flora et al. 2012).

Inverse correlations of hepcidin with eGFR, serum iron, and haemoglobin concentrations in subjects with CKD (Jiang et al., 2007) indicate that increased hepcidin levels are associated with lower kidney function and a lowered capacity to control anaemia. These findings suggest that hepcidin-based therapies or reduced lead exposure could benefit the CKD population. This study also provides key insights into the interaction between biochemical changes associated with CKD and lead-induced hepcidin dysregulation and renal injury, facilitating further clarification and designing more specific future studies and therapeutic interventions. (Agarwal et al., 2019).

The high serum hepcidin levels in CKD patients likely reflect a kidney deficiency, evidenced by the close correlation with serum creatinine and eGFR. A close relationship between lead and hepcidin supports the idea that lead can proliferate hepcidin dysregulation in chronic kidney disease. Moreover, we found significant dysregulation of iron metabolism in our cohort, characterized by lower serum iron and haemoglobin levels (Cerdá et al., 2017), which supports the role of hepcidin in CKD-associated anaemia.

Hepcidin levels and lead exposure are essential in CKD. The correlations observed between hepcidin, lead, and the other biochemical parameters strongly correlate with CKD development and manifestations and provide insight into their pathophysiology. Finally, additional investigations should assess the therapeutic approaches to hepcidin modulation and lead exposure that can be employed in managing CKD (Global Burden of Disease Study, 2013; Rhee et al., 2015).

It has been highlighted from this study that lead exposure and hepcidin dysregulation are essential contributors to the progression of CKD. In conclusion, our results show significantly higher serum hepcidin and blood lead levels in Egyptian CKD patients than in healthy controls. The relationship between high serum hepcidin and elevated blood lead concentrations in subjects with chronic kidney disease (CKD) indicates a complex situation in which lead exposure may exacerbate hepcidin dysregulation pathways and lead to accelerated progression of CKD. Significant associations were observed between high levels of hepcidin and clinically impaired kidney function, as shown by high levels of serum urea and creatinine and low eGFR. It shows that hepcidin mediates defects in chronic kidney disease (CKD) anaemia and iron metabolism.

Furthermore, the negative correlations between serum iron and haemoglobin levels and hepcidin levels confirm that hepcidin is the agent of CKD anaemia. The study's results indicated that lead exposure increased hepcidin and its effects on iron metabolism, aggravating the anaemia condition of people with CKD [19]. The association of higher lead with hepcidin levels especially demonstrated potential mechanisms in which environmental pollutants could influence the progression of CKD.

This study underscores the importance of ongoing monitoring of lead exposure, hepcidin levels and their possible interaction among CKD patients to provide a more comprehensive understanding of their impact on disease progression. These results underscore the importance of addressing lead within the context of CKD as an avoidable risk factor and suggest that disrupting lead's modulation of hepcidin may be a therapeutic opportunity to improve CKD outcomes. Moreover, future studies should target therapeutics that correct hepcidin dysregulation and ameliorate lead poisoning, each contributing factor to CKD progression, to develop new patient care strategies that slow CKD progression.

CONCLUSION

Hepcidin dysregulation and lead exposure may contribute to CKD. Elevated serum hepcidin levels have been identified in patients with CKD, associated both with impaired renal function and increased lead exposure, both leading to altered iron homeostasis and anaemia. Hepcidin and lead levels in CKD patients may provide valuable information regarding disease progression and potential therapeutic targets. Further studies are needed to investigate therapeutics targeting hepcidin modulation and reduced lead exposure to improve clinical manifestation in patients with CKD. These findings contribute to an increasingly large literature describing the interrelationship between environmental toxins, metabolic dysregulation and disease pathogenesis.

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