

Original Research Article

Depression but not anxiety is associated with iron deficiency anemia for patients with stage 2-4 CKD

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ABSTRACT

Background: Chronic kidney disease (CKD) is a global health challenge, often complicated by iron deficiency anemia (IDA), depression, and anxiety. While the impact of IDA on depression has been well-documented, its association with anxiety in non-dialysis-dependent CKD patients remains unclear. This study aimed to investigate the relationship between IDA and neuropsychiatric disorders, specifically depression and anxiety, in patients with non-dialysis-dependent CKD stages 2-4.

Methods: A cross-sectional study was conducted in the outpatient nephrology clinic at Gazi University Hospital, enrolling 200 patients with stable CKD (stages 2-4). Depression and anxiety were measured using the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI), respectively. Statistical analysis included comparisons of BDI and BAI scores between anemic and non-anemic groups, along with subgroup analysis of iron-treated anemic patients.

Results: Anemia was present in 38% of patients, and anemic patients had significantly higher BDI scores (mean 13.4 vs. 9.0, $p < 0.001$) than non-anemic patients, indicating a greater prevalence of depressive symptoms. No significant differences were found in BAI scores between the groups. However, anemic patients receiving iron supplementation had lower BDI and BAI scores compared to untreated anemic patients ($p < 0.001$).

Conclusions: IDA was associated with a higher prevalence of depression but not anxiety in non-dialysis CKD patients. Iron supplementation may help mitigate depressive symptoms in this population. Further prospective studies are needed to explore the full potential of iron therapy in managing mental health outcomes in CKD patients.

Keywords: Anxiety, Chronic kidney disease, Depression, Iron deficiency anemia, Iron supplementation

INTRODUCTION

Chronic kidney disease (CKD) represents a significant global health burden, affecting millions worldwide and leading to progressive kidney function loss.¹ In non-dialysis-dependent stages 2-4 CKD, patients often experience substantial declines in health-related quality of life due to complications such as anemia and neuropsychiatric disorders, including depression and anxiety.²

Anemia, particularly iron deficiency anemia (IDA), affects up to 50% of individuals in later CKD stages due to impaired erythropoiesis and chronic inflammation.³ Depression and anxiety are also prevalent, with significant impacts on quality of life and clinical outcomes.^{4,5} Untreated, these disorders lead to increased healthcare utilization and poorer health outcomes.⁶

Iron plays a critical role in brain function and neurotransmitter synthesis, and its deficiency is linked to neuropsychiatric symptoms, as seen in non-CKD

populations.^{7,8} Despite the established link between IDA and psychiatric disorders in the general population, limited research has explored this relationship in non-dialysis-dependent CKD patients. Most studies focus on hemodialysis patients, where the relationship between anemia and neuropsychiatric complications is well-documented.^{9,10}

This study aims to investigate the impact of IDA on depression and anxiety in CKD stages 2-4, filling this gap in the literature and informing better clinical practices to improve both mental and physical health outcomes in CKD patients.

METHODS

Study design

This cross-sectional study was conducted at the outpatient nephrology clinic of Gazi University Hospital from February to June 2023. Random sampling was used to include patients with stable stage 2-4 CKD, defined as an estimated glomerular filtration rate (eGFR) between 15-59 mL/min/1.73 m² and no recent medication changes or hospitalizations. The aim of this study was to evaluate the association between iron deficiency anemia (IDA) and neuropsychiatric disorders, specifically depression and anxiety, in non-dialysis-dependent CKD patients. The sample size was determined based on a prevalence estimate of IDA and its expected impact on neuropsychiatric health.

Inclusion criteria

Inclusion criteria were patients aged 18 years or older, with CKD stages 2-4 as defined by an eGFR of 15-59 mL/min/1.73 m², and stable renal function without dialysis dependence.

Exclusion criteria

Exclusion criteria included: Acute kidney injury or recent decompensation, hematological or solid malignancies, recent psychological trauma, diagnosed psychiatric conditions such as schizophrenia, major depression, or bipolar disorder, current use of antidepressants, antipsychotics, or erythropoiesis-stimulating agents (EPO), other causes of anemia, such as B12, folate, or copper deficiencies, chronic liver disease or autoimmune disorders that could influence anemia or mental health.

Data collection

Data were collected via face-to-face interviews conducted by trained healthcare personnel during the patient's clinic visit. Medical records were reviewed to confirm clinical and laboratory data. Depression and anxiety levels were measured using validated Turkish versions of Beck's Depression Inventory (BDI) and Beck's Anxiety Inventory

(BAI). Both BDI and BAI were administered in a single session.

Assessment tools

Beck's Depression Inventory (BDI): A 21-item self-report questionnaire assessing the severity of depression symptoms, with scores ranging from 0 to 63. Scores of 0-13 indicate minimal depression, 14-19 mild depression, 20-28 moderate depression, and 29-63 severe depression. The BDI has been validated for use in Turkish populations.¹¹

Beck's Anxiety Inventory (BAI): A 21-item self-report questionnaire that assesses the severity of anxiety symptoms. Scores range from 0 to 63, with 0-7 indicating minimal anxiety, 8-15 mild anxiety, 16-25 moderate anxiety, and 26-63 severe anxiety. The BAI is validated in the Turkish population.¹²

Statistical analysis

Descriptive statistics were used to summarize baseline characteristics (mean and standard deviation for continuous variables, frequencies and percentages for categorical variables).

The required sample size for achieving reliable internal consistency, as determined by Cronbach's alpha, is calculated to be 189 participants. We rounded this number to 200 to make up for any calculation errors.

Student's t-test was employed to compare mean BDI and BAI scores between the anemic and non-anemic groups. Univariate analysis was conducted to assess the relationship between BDI scores and key variables such as hemoglobin levels, transferrin saturation, and ferritin levels. Due to the limited sample size, multivariate analysis was not performed.

All analyses were performed using SPSS version 23.0 (IBM Corp), and a p-value of <0.05 was considered statistically significant.

RESULTS

A total of 200 patients with stable stage 2-4 chronic kidney disease (CKD) were included in the final analysis. Demographic and clinical baseline data is available at Table 1. Among them, 74 patients (38%) were classified as anemic, while 126 (62%) were non-anemic. The baseline characteristics of these two groups were compared, revealing significant differences in age, glomerular filtration rates (GFR), and CKD stage distribution.

As shown in Table 1, the anemic group was significantly older than the non-anemic group (mean age: 58.9±16.2 years vs. 52.9±17.6 years, p<0.01) and had significantly lower GFR values (mean GFR: 40.9±19.8 mL/min/1.73 m²

vs. 51.9 ± 20.5 mL/min/ 1.73 m^2 , $p < 0.01$). The non-anemic group had a higher proportion of patients in CKD stage 2 (35% vs. 18%, $p < 0.05$), whereas the anemic group had a larger percentage of patients in CKD stage 4 (41% vs. 18%, $p < 0.05$).

Table 1: Demographic data of the patients.

Characteristic	Value	Ratio, %
Age (years $\pm$ SD)	55 $\pm$ 17	NA
Gender (female/male)	94/106	47/53
Marital status (married/nonmarried)	140/60	70/30
Smoker/non-smoker	56/142	28.3/71.7
Diabetes (present/absent)	53/147	26/74
Hypertension (present/absent)	167/33	83/17
Coronary artery disease (present/absent)	20/180	10/90
Cerebrovascular incident (present/absent)	4/196	2/98

Depression was assessed using the Beck Depression Inventory (BDI). Anemic patients had significantly higher BDI scores compared to non-anemic patients (mean BDI: 13.4 ± 9.8 vs. 9.0 ± 7.1 , $p < 0.001$), indicating worse depression levels in the anemic group. Using a BDI cut-off score of 11, 51.4% of anemic patients required further evaluation for clinical depression, compared to 31.7% of non-anemic patients ($p = 0.007$).

Univariate analysis of the anemic group revealed no significant relationship between depression scores (BDI) and parameters such as hemoglobin levels, transferrin saturation, or ferritin levels ($p > 0.05$ for all). However, subgroup analysis showed that anemic patients who were treated with iron had significantly lower BDI scores compared to untreated anemic patients (6.0 ± 4.0 vs. 16.9 ± 11.1 , $p < 0.001$), suggesting a potential benefit of iron supplementation for depressive symptoms.

Table 2: Selected baseline characteristics.

Characteristic	Non-anemic (n=126)	Anemic (n=74)	P value
Age (years)	52.9 $\pm$ 17.6	58.9 $\pm$ 16.2	<0.01
GFR (mL/min)	51.9 $\pm$ 20.5	40.9 $\pm$ 19.8	<0.01
CKD stage 2 (%)	44 (35)	14 (18)	<0.05
CKD stage 3 (%)	58 (47)	30 (41)	NS
CKD stage 4 (%)	22 (18)	30 (41)	<0.05

Anxiety was measured using the Beck Anxiety Inventory (BAI). There was no significant difference in BAI scores between the anemic and non-anemic groups (mean BAI: 11.4 ± 9.9 vs. 9.7 ± 6.5 , $p = 0.16$). The frequencies of minimal, mild, moderate, and severe anxiety were similar in both groups. However, in the subgroup of anemic patients, those who received iron treatment had

significantly lower BAI scores compared to untreated anemic patients (mean BAI: 6.5 ± 5.1 vs. 20.5 ± 8.2 , $p < 0.001$), indicating that iron supplementation may have a beneficial effect on anxiety symptoms. Data presented at Table 2, Table 3 and Table 4; respectively.

Table 3: Univariate analysis of BDI scores.

Parameter	R value	P value
Hemoglobin	-0.12	0.28
Transferrin saturation	-0.08	0.45
Ferritin	-0.15	0.20

Table 4: Distribution of anxiety and depression severity by anemia status.

Severity	Non-anemic (n=126) (%)	Anemic (n=74) (%)	P value
Minimal anxiety	56 (44)	30 (40)	0.72
Mild anxiety	50 (40)	28 (38)	
Moderate anxiety	14 (11)	10 (14)	
Severe anxiety	6 (5)	6 (8)	
No depression	86 (68)	36 (49)	0.006
Depressed	40 (32)	38 (51)	

Table 5: Subgroup analysis of treated vs untreated anemic patients.

Characteristic	Untreated anemia (n=36)	Treated anemia (n=40)
BDI score	16.9 $\pm$ 11.1	6.0 $\pm$ 4.0
BAI score	20.5 $\pm$ 8.2	6.5 $\pm$ 5.1

DISCUSSION

This study demonstrates that anemia is significantly associated with higher BDI scores in CKD patients, indicating a greater prevalence of depressive symptoms among those with anemia. However, no significant link was found between anemia and anxiety based on BAI scores. These findings suggest that IDA may play a role in the development of depressive symptoms in non-dialysis CKD patients, encouraging further research on the effects of iron supplementation therapy.

The relationship between anemia and depression in CKD patients has been well-documented. For instance, a study from Trinidad and Tobago highlighted anemia as a major predictor of depression, stressing the importance of mental health screening in this patient group.⁵ This supports our findings, as we observed higher depression scores in anemic CKD patients. Tsai et al demonstrated that depressive symptoms are associated with faster progression of CKD.¹³ This finding suggests that treating depression in CKD patients could slow disease progression, further supporting the need for comprehensive mental health screening in CKD populations.

Additionally, research from China has explored the bidirectional relationship between CKD and depression, showing how these two conditions can exacerbate one another, ultimately leading to poorer health outcomes.¹⁴ This study further emphasizes this interaction, highlighting the importance of addressing both anemia and depression to improve patient outcomes.

The potential for iron supplementation to improve psychiatric symptoms has been demonstrated in several studies. For example, researchers in South Korea found that addressing iron deficiency significantly reduced depressive symptoms.^{7,15} Although this study did not directly evaluate the effects of iron supplementation, our observation that anemic patients receiving iron treatment had lower BDI scores supports this conclusion.

Despite our primary findings showing no significant association between IDA and anxiety, other studies suggest a possible link. A genetic study utilizing Mendelian randomization, for example, indicated that improving iron levels might reduce the risk of anxiety disorders.⁸ This offers a new perspective on iron's role in managing anxiety, particularly in CKD patients, and warrants further exploration.

In studies focusing on hemodialysis patients, anemia has been identified as a factor that significantly affects mental health and quality of life. Several studies, which evaluated the mental well-being of hemodialysis patients, emphasized that addressing anemia could lead to improved anxiety and depression outcomes.^{9,16,17}

Although substantial evidence links iron deficiency to mental health outcomes in the general population, further research is needed to clarify the role of iron in CKD populations. Berthou and colleagues discussed the neurobiological effects of iron on mood and cognitive function, findings that are relevant to understanding the broader implications for CKD patients.¹⁸

Finally, despite the growing evidence supporting the relationship between anemia and depression, several gaps remain in our understanding of how iron supplementation affects mental health outcomes in non-dialysis CKD patients. Future research should focus on determining whether iron supplementation alone can sufficiently alleviate depressive symptoms, or whether a combination of treatments is necessary.

Our study has limitations, including its sample size and observational design, which restricts the ability to draw definitive conclusions. Potential biases and confounding factors may have influenced the results, and the cross-sectional nature of the study limits causal inferences. Future studies should employ prospective designs to explore the effects of iron supplementation on mental health outcomes in non-dialysis CKD patients, while also considering different treatment strategies for managing both anemia and mental health.

CONCLUSION

In conclusion, our findings suggest a potential association between IDA and depression in non-dialysis CKD patients, though no significant link with anxiety was identified. The potential benefits of iron supplementation for improving mental health outcomes should be further investigated through well-designed prospective studies. Effective anemia management, alongside comprehensive mental health screening, may improve the quality of life for CKD patients.

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