Journal of
Kerman University of Medical Sciences

https://jkmu.kmu.ac.ir
doi:10.34172/jkmu.4089
JKMU 2026;33:4089

Original Article

Evaluation of Hemoglobin and Urea Levels in Chronic Renal Failure Patients with and without Diabetes Referred to Rafsanjan Clinic 2021–2022

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Abstract

Introduction: This study investigated hemoglobin concentration in chronic renal failure (CRF) patients with and without diabetes referred to the Rafsanjan Diabetes Clinic from 2021 to 2022.

Methods: In this descriptive study, 112 patients with chronic renal failure from the diabetes clinic at Ali-ibn Abi-Talib Hospital were selected using a convenience sampling method and examined. Chronic kidney disease patients not undergoing hemodialysis were included, and patients with specific blood conditions, a history of blood transfusions, or incomplete records were excluded. Demographic and clinical parameters were collected using a researcher-made checklist. SPSS 24 software was used for data analysis.

Results: In this study, 120 CRF patients, averaging 63.90 years old, were evaluated, divided into two groups: those with ($n=64$) and those without ($n=56$) diabetes. Results indicated that diabetic patients had significantly higher body mass index and a higher mean age compared to non-diabetic patients ($P<0.001$). Laboratory analyses revealed that the diabetic group showed elevated levels of urea, HbA1c, and fasting blood sugar, higher rates of anemia, and reduced levels of hemoglobin (all $P<0.001$). A logistic regression analysis revealed that diabetes significantly increases the risk of developing anemia among CRF patients, nearly tripling the likelihood (OR=3.110, $P=0.494$).

Conclusion: The results showed that CRF in patients with diabetes was associated with disorders such as lower hemoglobin levels, anemia, and higher HbA1c. Even though this disorder itself can cause adverse effects in diabetic patients, it is necessary to continuously evaluate the mentioned indicators in these patients, since in the long term, they will aggravate the symptoms and severity of the disease.

Keywords: Renal insufficiency, Hemoglobin, Hemoglobin a glycosylated, Diabetes mellitus, Urea

Citation: Jamshidi M, Kamiab Z, Karimi Fard M, Shafiepour M, Bazmandegan G. Evaluation of hemoglobin and urea levels in chronic renal failure patients with and without diabetes referred to Rafsanjan clinic 2021–2022. Journal of Kerman University of Medical Sciences 2026;33:4089. doi:10.34172/jkmu.4089

Received: August 18, 2025, **Accepted**: November 2, 2025, **ePublished**: April 18, 2026

Introduction

Kidney failure is caused by various diseases that cause a significant reduction in the structure or function of the kidneys. If kidney damage and decreased function (measured by glomerular filtration rate (GFR)) persist for three months, it is considered chronic renal failure (CRF) (1). This disease is classified based on proteinuria, histopathological studies, and often based on GFR. Patients who have had a GFR < 60 mL/min/1.73 m^2 for the past 3 months are considered to have CRF, irrespective of kidney damage. The most important causes of CRF are long-term diabetes and hypertension (1). Less common causes include glomerulonephritis, interstitial nephritis, polycystic kidney, pyelonephritis, long-term urinary tract obstruction due to stones, prostatic hypertrophy, and heavy metal poisoning (1).

Patients with CRF experience various complications throughout their lives. One of these complications is anemia. The association between decreased kidney function and anemia is well known (2). Anemia has a high prevalence in CRF patients and worsens with the progression of kidney failure. According to the National Health and Nutrition Examination survey, eGFR < 60 increases the prevalence

of anemia, and in GFR < 30 mL/min/1.73 m^2, anemia is considered a common and severe complication of CRF. Reduction of RBC lifespan, malabsorption of iron and vitamin B12, increase in tubulointerstitial damage, reduction of erythropoietin, and possibly inflammation are the main factors contributing to anemia in CRF (3, 4).

Diabetes is a clinical syndrome that occurs due to a decrease or lack of insulin, causing abnormal carbohydrate metabolism and subsequent hyperglycemia. Clinically, it is classified as either type 1 or type 2 diabetes, with approximately 85% of cases falling under type 2 diabetes (5). Diagnosing diabetes is based on fasting plasma sugar, blood glucose 2 hours after a meal, random blood sugar, and glycosylated hemoglobin (HbA1C). HbA1C is the result of the non-chemical enzymatic reaction of Hb with glucose and reflects the average blood sugar in the last 2–3 months(1). It is the best way to assess blood sugar, and its monitoring and control can reduce the incidence and progression of diabetes complications. Diabetes is the leading cause of CRF worldwide (6). Diabetic nephropathy is a glomerulopathy characterized by structural and functional changes in the kidneys. The most significant structural changes include extensive mesangial enlargement, glomerular basement membrane thickening, and glomerulosclerosis (6).

Diabetic nephropathy is widely recognized as the leading cause of kidney disease globally, as evidenced by numerous studies. Several factors contribute to a heightened risk of developing this condition, including advancing age, genetic predisposition, elevated blood sugar levels, abnormal lipid profiles, high blood pressure, impaired glomerular filtration rate (GFR), smoking, and obesity. Approximately 40% of individuals with diabetes—both type 1 and type 2—experience nephropathy. However, in most cases, approximately 90% have type 2 diabetes compared to just 10% for type 1 diabetes (3). Anemia is defined as a deficiency in the oxygen-carrying capacity of the plasma and is defined as Hb < 12 g/dL in non-pregnant women and Hb < 13 g/dL in men (7). The prevalence of anemia in diabetic people who are in stage 3 of CRF is three times that of non-diabetic people, and diabetic men are more prone to anemia than diabetic women. There is an inverse and significant relationship between erythropoietin levels and HbA1C (2).

It has been observed that diabetic patients with normal kidney function have lower Hb levels than non-diabetic patients (8). Moreover, compared to non-diabetic people, anemia occurs earlier in diabetic nephropathy (9, 10) and is more severe in higher stages of CRF and albuminuria (11). Kidney damage with tubulointerstitial tissue involvement leads to an inadequate increase in erythropoietin levels in response to reduced hemoglobin (11). Several mechanisms explain anemia in the early stages of kidney failure in diabetic patients, including the following:

1. The adverse effect of diabetes on the interstitial space of the kidney tissues and the damage to peritubular fibroblasts that produce erythropoietin.
2. Systemic inflammation associated with diabetes.
3. Autonomic neuropathy associated with diabetes disrupts the function of erythropoietin-producing renal cells, making accurate diagnosis and assessment of anemia difficult.
4. In patients with autonomic neuropathy, the basal level of erythropoietin decreases in response to hypoxia.
5. Decreased RBC survival.
6. The use of drugs such as rosiglitazone and metformin, ACE I, ARB, and aspirin.

Anemia is a significant risk factor that contributes to the progression of chronic renal failure (CRF) and various complications associated with diabetes. Early treatment of anemia in these patients can slow down the progression of kidney failure, reduce complications, and improve patient survival (12). Given the significance of the issues raised and the widespread occurrence of chronic kidney diseases among diabetic patients, this study examined hemoglobin levels in diabetic and non-diabetic individuals who visited Rafsanjan Diabetes Clinic with kidney failure during 2021–2022.

Methods

Participants and study design

This descriptive study focused on patients with chronic kidney disease who were referred to Rafsanjan Diabetes Clinic. A total of 112 patients were included in the research (56 people in each group) using the sample size formula below, based on the study results by Clement Lo et al. (13):

$$n = (z_{1-\alpha/2}+z_{1-\beta})^{2^*} (\sigma_1^2+\sigma_2^2)/(\mu_1-\mu_2)^2$$

In this equation, the value of $Z1 - \alpha / 2$ is 1.96. δ_1 (1.5) is the estimated standard deviation of hemoglobin levels in individuals with diabetes. δ_2 (1.2) is also the estimated standard deviation for hemoglobin levels in the general population. The minimum clinically significant difference has been identified as 1 g/dl.

The convenience sampling method was utilized while carefully considering the inclusion and exclusion criteria.

The patients eligible for inclusion were those with chronic kidney failure who were not receiving hemodialysis and had completed the informed consent process. Individuals with a history of hemoglobinopathy, iron deficiency, recent blood transfusion within the past three months, previous kidney transplant, life-threatening conditions like cancer, disorders involving high cell turnover such as IBD, or cases where file information was incomplete were excluded from the study (1).

All patients involved in the study provided informed consent. The study received approval from the Ethics Committee of Rafsanjan University of Medical Sciences under the ethics code IR.RUMS.REC.1400.079. Patient information was collected through the registry of patients with CRF referred to Rafsanjan Diabetes Clinic (southeast of Iran) from April 2021 to March 2022 using a researcher-made checklist. Study variables, including gender (female, male), weight (kg), age, height (cm), body mass index (BMI) (kg/m^2), waist circumference (cm), diastolic and

systolic blood pressure (mmHg), CRF stage, BUN, Cr, FBS, Hb, and HbA1c, were collected.

In this study, CRF and diabetes were diagnosed by a nephrologist based on diagnostic criteria. CRF was identified as GFR ≤ 89 mL/min/1.73 m^2, and kidney failure staging was calculated using the MDRD formula. CRF stages were defined according to NKF/KDOQI guidelines as follows: first stage GFR ≥ 90, second stage GFR = 60–89, third stage GFR = 30–59, fourth stage GFR = 29–15, and fifth stage GFR < 15. (12)

MDRD: eGFR

$(mL/min/1.73m^2) = 186 \times (Pcr^{-1.154}) \times (Age^{-0.203}) \times (0.742$ if female) × (1.212 if Black)

The National Kidney Foundation/Kidney Disease Outcomes Quality Initiative (NKF/KDOQI) guidelines were used to evaluate anemia. According to these guidelines, anemia is defined as hemoglobin levels below 12 g/dL in men and postmenopausal women over the age of 50 and below 11 g/dL in premenopausal women under 50 (14). HbA1C was examined in all patients, and patients with HbA1C > 6.4% were considered diabetic (3, 5).

Statistical analysis

Statistical analyses were performed using SPSS software version 24.0 (IBM SPSS Inc., Chicago, IL, USA) and the SAS statistical package version 9.2 for Windows (SAS Institute Inc., Cary, NC, USA). Numerical variables were summarized as mean ± standard deviation (SD) with accompanying range or median (1^{st} quartile–3^{rd} quartile), while categorical variables were described in terms of frequency and percentage. For comparisons, independent *t*-tests were utilized for numerical data with normal distribution, whereas the non-parametric Mann–Whitney *U* test was used for data with non-normal distribution. To examine the relationship between hemoglobin levels and diabetes in patients with kidney failure, both univariate and multivariate linear and logistic regression models were employed. Adjustments for potential confounding variables, such as age, sex, BMI, BUN, and GFR, were made if their *p*-value in the univariate analysis was ≤ 0.20. The regression outcomes were presented as odds ratios (OR) or unstandardized coefficients (B), along with 95% confidence intervals (CIs). Statistical significance was defined by two-tailed *P*-values, with a threshold of $P \leq 0.05$.

Results

In our study, 120 CRF patients with a mean age of 63.90 ± 14.22 were examined. The patients were categorized into two groups: those with a history of diabetes (64 people) and those without a history of diabetes (56 people). The distribution of clinical and demographic variables in the two groups is compared in Table 1. According to the results, in people with a history of diabetes, the mean age and BMI ($P = 0.001$ and $P = 0.014$) as well as the frequency of female gender were significantly higher ($P = 0.003$).

A comparison of laboratory findings between patients with kidney failure, with and without a history of diabetes, revealed statistically significant differences. In diabetic patients, the mean urea levels, HbA1c, and FBS were significantly higher ($P = 0.001$ for all). Additionally, the frequency of anemia and the proportion of patients with HbA1c > 6.5% were significantly higher in the diabetic group compared to the non-diabetic group ($P = 0.004$ and $P = 0.001$, respectively). The average GFR and hemoglobin levels were significantly reduced among diabetic patients as opposed to those without diabetes ($P = 0.001$ for both). Specific findings are outlined in Table 2.

Table 3 presents the outcomes of univariate and multivariate linear and logistic regression analyses examining the correlation between hemoglobin levels and diabetes in individuals with kidney failure. These analyses were adjusted for variables like age, sex, BMI, BUN, and GFR. The refined logistic regression model indicates that the presence of diabetes elevates the risk of developing anemia more than threefold (OR = 3.110, $P = 0494$).

Discussion

Although CRF does not have any specific symptoms in the primary stages of the disease, it gradually becomes apparent with a reduction in renal function and the occurrence of symptoms like fatigue, muscle cramps, and loss of weight. Anemia is a common complication in patients with CRF, which is accompanied by decreased quality of life, increased morbidity, and higher mortality rates (15, 16).

The results of the present study revealed that in patients with CRF who had a history of diabetes, hemoglobin levels were lower, and anemia was significantly higher. Also, a history of diabetes in participants with CRF more than tripled the risk of developing anemia. Anemia stands out as one of the most prevalent and clinically important complications of CRF, often linked to a heightened risk of mortality, hospitalization, and development of cardiovascular disease risk factors (17). The progression of this disease serves as a significant risk factor for anemia, whose likelihood increases as chronic renal failure (CRF) advances. Research indicates that the prevalence of anemia is approximately 73% in patients at stage 3 of CRF, 87.3% in those at stage 4, and rises to 93% in individuals at stage 5 (18, 19). The results of the study by Stauffer et al. showed that the prevalence of anemia in people with CRF is 15.4%, which is twice that of the general public (7.6%). Anemia becomes progressively more common as chronic renal failure (CRF) advances, rising from 8.4% in patients at stage 1 to 53.4% in those at stage 5. In the present study, 22.8% of the participants had visited medical centers for the treatment of anemia in the last three months (20). Bonakdaran et al. reported that diabetic patients with moderate kidney failure had a significantly higher incidence of anemia than diabetic patients with mild kidney failure, and the presence of albuminuria was also associated with anemia. The kidneys play a crucial role in producing red blood cells when blood oxygen levels drop. Erythropoietin is released, serving as a signaling molecule that promotes the production of red blood cells. Any disruption in this mechanism can lead to anemia (21). Iron deficiency, inflammation, and the buildup of

Table 1. Demographic characteristics

Variable	Total (N=112)	Diabetes (Yes, n=56)	Diabetes (No, n=56)	OR (95% CI)	*P*-value
Age (years)	63.90±22.14 (30–89)	68.36±10.41 (41–89)	58.80±16.28 (30–89)	1.54 (1.23–1.85)	0.001*
Gender Female	48 (45%)	31 (55.8%)	17 (30.4%)	3.41 (1.17–6.91)	0.003†
Male	64 (55%)	25 (44.2%)	39 (69.6%)		
Height (cm)	171.38±10.09 (148–190)	170.58±9.69 (150–189)	172.30±10.55 (148–190)	0.983 (0.84–1.19)	0.253*
Weight (kg)	77.88±10.36 (48–98)	79.09±9.56 (54–98)	76.50±11.12 (48–98)	1.25 (0.98–1.62)	0.271*
BMI (kg/m²)	26.57±3.3 (16.61–34.22)	27.24±3.10 (20.20–34.22)	25.79±3.32 (16.61–31.25)	1.61 (1.26–2.13)	0.014*
BMI group Underweight	3 (2.6%)	0 (0%)	3 (5.4%)		
Normal	62 (55.3%)	46 (82.1%)	16 (28.6%)	-	0.840†
Obese	47 (41.9%)	10 (17.9%)	37 (66.1%)		
CRF stage Stage 2	11 (10%)	5 (8.9%)	6 (10.7%)	Reference	
Stage 3	61 (54.2%)	33 (58.9%)	28 (50%)	1.738 (0.90–6.15)	0.656†
Stage 4	27 (24.2%)	14 (25%)	13 (23.2%)	1.500 (0.85–5.40)	
Stage 5	13 (11.7%)	7 (12.5%)	6 (10.7%)	1.867 (0.92–8.94)	

Data are expressed as mean±standard deviation (min-max) or *n* (%). OR: odds ratio; CI: confidence interval; BMI: body mass index; CRF: chronic renal failure; **p*-value was derived using an independent two-sample *t*-test, as the data followed a normal distribution; †*p*-value was derived from chi-square test

Table 2. Laboratory parameters

Variable	Total (N=112)	Diabetes (Yes, n=56)	Diabetes (No, n=56)	OR (95% CI)	*P*-value
BUN (mg/dL)	48.50 (34.25–71.50)	52.00 (43.50–75.00)	36.50 (28.00–50.00)	1.11 (1.02–1.21)	0.001*
Creatinine (mg/dL)	2.10 (1.70–2.88)	2.19 (1.73–2.70)	2.05 (1.70–3.18)	0.997 (0.829–1.20)	0.914†
HbA1c (%)	6.45 (5.80–8.50)	8.25 (7.50–9.28)	5.70 (5.60–5.80)	-	0.001*
Fasting blood sugar (mg/dL)	105.00 (95.00–156.75)	154.00 (119.25–208.50)	95.00 (95.00–102.00)	1.29 (1.25–1.53)	0.001†
GFR (mL/min/1.73 m²)	17.58±16.36 (4.5–0.88)	16.33±19.34 (6.0–76.8)	18.81±13.41 (4.5–0.88)	0.986 (0.966–1.007)	0.191†
Hemoglobin (Hb) (g/dL)	12.81±2.90 (5.5–22.6)	12.11±2.39 (5.5–22.6)	13.60±3.23 (9.5–19.8)	0.823 (0.715–0.974)	0.004†
Hemoglobin group Normal	61 (55.8%)	26 (46.3%)	35 (62.5%)	2.05 (1.18–6.96)	0.004ǂ
Anemia	52 (44.2%)	30 (53.7%)	21 (37.5%)		
HbA1c group Normal	57 (50.8%)	5 (8.9%)	52 (100%)	-	0.001ǂ
>6.5%	55 (49.2%)	51 (91.1%)	(0%)		

Data are expressed as mean±standard deviation (SD), median (1st quartile–3rd quartile), or *n* (%). OR: odds ratio; CI: confidence interval; HbA1C: hemoglobin A1c; GFR: glomerular filtration rate; * *P*-value was derived from non-parametric Mann–Whitney *U* test because of skewed distribution; †*P*-value is derived from independent two-sample *t*-test because of normal distribution; ǂ*P*-value is derived from chi-square test

Table 3. Association between hemoglobin and diabetes in patients with kidney failure using logistic or linear regression models (*n*=120)

Variable	Unadjusted			Adjusted*		
	Effect size	95% CI	p-value	Effect size	95% CI	*P*-value
Diabetes (Binary: normal vs. anemia)	OR=2.949	1.676 to 3.881	0.049	OR=3.110	0.964 to 9.406	0.494
FBS (continuous)	B=−1.497	−2.178 to −0.478	0.043	B=−0.786	−1.839 to 0.266	0.142

OR: odds ratio was derived from a logistic regression model, with hemoglobin level treated as a binary variable, including normal or anemia
CI: Confidence interval
B: Unstandardized coefficient was derived from a linear regression model, with hemoglobin level treated as a quantitative variable
* Adjusted for age, gender, BMI, BUN, and GFR.

uremic toxins are potential contributors to anemia in patients with chronic renal failure (CRF). This condition can lead to various complications, including cognitive impairment, sleep disturbances, accelerated disease

progression, cardiovascular issues, and a heightened risk of mortality (21, 22). Although diabetes is one of the leading causes of kidney involvement and failure, anemia in these patients is more common and even worse than in non-diabetic patients at any GFR level (11). Among various populations, the prevalence of anemia in individuals with diabetes has been documented to range between 13% and 46.5% (23, 24). Although CRF does not play a role in all cases of anemia in diabetic patients, the interaction between factors such as reduced kidney function, lack of synthesis and release of erythropoietin, nutritional disorders, chronic inflammation, iatrogenic causes, and infectious diseases makes anemia appear earlier and more severely in diabetic patients (8, 25).

The study's findings indicate that the average urea levels were notably elevated in CRF patients who had a history of diabetes. Similarly, research conducted by Kene et al. revealed a 43.2% and 18.8% prevalence of creatinine and urea abnormalities in these individuals, respectively. Furthermore, the study highlighted a significant association between urea disorders and factors such as the duration of diabetes and alcohol consumption (26). Koppe et al. highlighted that urea has the potential to disrupt β-cell glycolysis and impair insulin secretion in cases of chronic renal failure (CRF) (27). In the study by Kamal et al, it was noted that disturbance in urea and creatinine levels due to the increase in blood glucose level indicates a decrease in kidney function in diabetic patients (28). Creatinine and urea disorders are among the indicators of CRF and the best guides for estimating the disease progress and prognosis, and creating nutritional restrictions for CRF patients with diabetes (26, 29). Uremic metabolites and toxins, which are usually excreted by the kidneys, gradually accumulate in CRF, and many of them adversely affect the body. Urea, as the primary uremic metabolite, typically exhibits low toxicity. However, it can indirectly impair cellular function by altering serum or tissue composition and directly contribute to increased oxidative stress, which interferes with glucose uptake in fat cells (30). A study found that administering urea to mice led to impaired insulin secretion, elevated levels of O-GlcNAcylation, and increased oxidative stress in conditions associated with chronic renal failure (CRF). In patients with CRF, high circulating urea levels disrupt glucose homeostasis by inhibiting glycolysis, ultimately reducing insulin secretion. Disorders in glucose homeostasis, which depend on sufficient insulin production by pancreatic β-cells and proper insulin activity in peripheral tissues, impact nearly half of CRF patients (27). The development of insulin resistance in these patients involves multiple mechanisms, including the role of β-cell dysfunction and its associated processes. Additionally, the uremic environment contributes to insulin resistance by disrupting the insulin degradation system in peripheral tissues. This factor is widely recognized as a key contributor to alterations in glucose homeostasis observed in chronic renal failure (CRF) (1).

The study findings indicated that the number of cases with HbA1c over 6.5 is significantly higher among CRF patients with a history of diabetes. In the study by Luk et al, during a follow-up period of about 7 years, patients who progressed to CRF had a higher mean level of HbA1c (31). Waden et al. observed that patients with end-stage renal disease (ESRD) showed higher mean and standard deviation values of HbA1c, both of which were associated with adverse cardiac and renal outcomes. Among individuals with type 1 diabetes, fluctuations in HbA1c levels served as a predictor for the development of microalbuminuria, the advancement of kidney disease, and the occurrence of heart disease events (32). Kang et al. showed that high levels of HbA1c, even in non-diabetic patients, may be associated with CRF and kidney function in patients with HbA1c levels and need to be monitored (33). HbA1c is used as an index to measure average blood glucose over several months and is the mainstay of blood glucose monitoring. Although it has limitations for patients with diabetes, CRF, and those undergoing dialysis (34), blood sugar monitoring is considered the cornerstone of diabetes care. The primary methods for evaluating the effectiveness of blood sugar control include self-monitoring of blood glucose (SMBG) and measurement of HbA1c (35). By preventing very low or high glycemic levels, blood sugar control reduces complications and mortality in diabetic patients with CRF (36). The main limitation of this study was the inability to determine the temporal relationship between diabetes and chronic renal failure (CRF), owing to its cross-sectional design.

Conclusion

The findings of this study indicate that CRF in patients with diabetes was associated with disorders such as lower hemoglobin level, anemia, elevated urea, and higher HbA1c. Even though this disorder itself can cause adverse effects in diabetic patients, it is necessary to continuously evaluate the mentioned indicators in these patients, since in the long term, it will aggravate the severity and symptoms of the disease. It is also suggested that these indicators be checked in care programs for CRF patients with diabetes.

Acknowledgements

The authors of this thesis are grateful to the Clinical Research Development Unit of Rafsanjan Ali-Ibn Abi-Talib Hospital for their cooperation and support in the implementation of the project.

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Competing Interests
The authors of the article have no conflict of interest.

Data Availability Statement
All necessary data will be available from the corresponding author upon reasonable request.

Ethical Approval
This study was approved by the Ethics Committee of Rafsanjan University of Medical Sciences, Rafsanjan, Iran (IR.RUMS.REC.1400.112).

Funding
This study did not receive any funding.

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