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Original Article

Do hemoglobin levels affect the progression of chronic kidney disease in patients with stage 3-4 chronic kidney disease?

Ali Riza Caliskan[1], Yasin Sahinturk[2], Aygul Ozdemir[3], Metin Sarikaya[4]

[1]Inonu University, Faculty of Medicine Department of Gastroenterology, Malatya, Turkey
[2]University of Health Sciences Antalya Training and Research Hospital, Department of Internal Medicine, Antalya, Turkey
[3]Dinar Public Hospital, Department of Internal Medicine, Afyonkarahisar, Turkey
[4]University of Health Sciences Antalya Training and Research Hospital, Department of Nephrology, Antalya, Turkey

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Abstract

Aim: We aimed in our study to evaluate the effect of anemia on renal progression in patients with stage 3-4 CKD.

Material and Methods: A total of 88 patients, 44 females, and 44 males, were followed up in a pre-dialysis outpatient clinic with a diagnosis of stage 3-4 CKD. Forty-four of these patients had hemoglobin (HGB) value above 12 g/dL, whereas 44 of them had a value between 10-12 g/dL. We accepted the first group as normal and the second group as mild anemia. We followed up the mild anemia group without Erythropoietin (EPO) treatment. Glomerular filtration rate (GFR) values were calculated with BUN, creatinine, hemoglobin, albumin and uric acid levels that had been measured in four months periods. GFR values were calculated using the MDRD formula. The follow-up duration of the two groups was twelve months.

Results: Initial, fourth, eighth and twelfth months GFR values of the patients were calculated. There was no significant difference ($F=1.242$, $p>0.05$) between the GFR values of first, fourth, eighth, and twelfth months controls. GFR values measured at four different times were similar. Also, the GFR values showed no difference between the HGB groups ($F=1.892$, $p>0.05$). HGB levels did not affect GFR values measured at different times.

Conclusion: It is thought that in stage 3-4 CKD, maintenance of-HGB level at 10-12 g/dL or above 12 g/dL had a similar effect on renal progression. During the follow-up of CKD, HGB level above 10 g/dL is sufficient for controlling the progression of CKD.

Keywords: Renal Anemia; Progression of Chronic Kidney Disease; Erythropoietin.

INTRODUCTION

Chronic Kidney Disease (CKD) is defined as a condition that affects the kidney, with the potential to cause either progressive loss of kidney function or complications resulting from decreased kidney function. CKD is thus defined as the presence of kidney damage or reduced level of kidney function for three months or more, irrespective of diagnosis (1). The rate of progression varies substantially. Several predisposing host factors may also contribute to the process. Treatments to delay progression are aimed at treating the primary disease and strictly managing the systemic blood pressure, proteinuria, calcium-phosphate metabolism, hyperparathyroidism, hyperlipidemia, acidosis, hyperuricemia, and anemia (2,3). End-stage renal disease (ESRD), which is characterized by progressive, irreversible loss of nephrons and a level of glomerular filtration rate (GFR) lower than 15 ml/min/1.73m², has an increasing incidence and prevalence (4).

Normochromic normocytic anemia becomes a frequent problem when the GFR is lower than 60 ml/min/1.73m² (5). Shortening the duration of life of erythrocytes due to uremic toxins from the kidneys, and decreased erythropoietin (EPO) production and bone marrow response to EPO are the leading causes of renal anemia (6). According to the KDIGO guideline in 2012, the target hemoglobin (HGB) level should be considered 11-12 mg/DI (7).

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Corresponding Author: Ali Riza Caliskan, Inonu University, Faculty of Medicine Department of Gastroenterology, Malatya, Turkey
E-mail: komamir308@gmail.com

GFR decline is expected to slow down by increasing the level of HGB, but the exact range of HGB for the best renal protection is not fully understood, and the literature has confounding results. In our research, we planned to study the effects of anemia on the progression of CKD in different HGB groups.

MATERIAL and METHODS

Patients followed in the Antalya Training and Research Hospital Nephrology Pre-dialysis clinic between May 2014 and April 2015, aged 18-80 and who had a GFR range of 15-60 ml/min/1.73m² were included in this retrospective study. A total of 1200 patient files were analyzed. Patients with coronary artery disease, malignant disease, ferritin <100 ng/ml, ferritin> 800 ng/ml, malnutrition, abnormal thyroid function tests, hematological diseases, obvious gastrointestinal system or gynecological bleeding were excluded. We had two groups of patients. The first group had a starting HGB level between 10-12 g/dL and the second group had a starting HGB level above 12 g/dL. For the first group, patients with a control HGB level lower or higher than group limits (10-12 g/dL) and for the second group, patients with a control HGB level lower than 12 g/dL were excluded from the study population. Finally, 88 CKD patients were included in this study. Forty-four patients had HGB levels between 10-12 mg/dL and the remaining 44 patients had HGB level over 12 mg/dL. Both groups received basic CKD treatment such as protein or salt restriction. Both groups also received angiotensin-converting enzyme inhibitor-angiotensin receptor blocker, vitamin D, phosphate chelator, uric acid lowering agent or essential amino acid replacement according to their treatment requirements. ACE / ARB drug use was similar in both groups. Patient GFR values were calculated with the MDRD formula (GFR=170x $[Pcr]^{-0,999}$ x $[Age]^{-0,176}$ x [0.762 for woman] x x $[SUN]^{-0,170}$ x $[Alb]^{-0,318}$) for four months intervals.

Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study which was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by the institutional ethics committee of Antalya Training and Research hospital (Date of Approval: 11/9/2014; Reference number: 46/6).

Statistical Analyses

Descriptive statistics are presented with frequency, percentage, mean and standard deviation values. Variance analyses were used to evaluate differences between HGB level normal and low groups. Relationships between categorical values were analyzed with the Bonferroni-Dunn test or Pearson chi-square test. The overall data were analyzed with the Statistical Package for the Social Sciences (SPSS) 20.0 and a p-value < 0.05 was considered statistically significant.

RESULTS

A total of 88 stages 3-4 CKD patients were included. Patient groups were homogeneous in terms of patient demographics (Table 1). Mean age was 62.2 (HGB ≤12 group 61.9; HGB>12 group 62.5). The youngest patient was 23, and the oldest was 80 years old. The mean starting HGB level of the HGB≤12 group was 11.4 mg/dL, and for the HGB>12 group this level was 14.2 mg/dL. The HGB level 10-12 g/dL group had 44 patients including 22 male and 22 female patients. The HGB>12 g/dL group also had 44 patients, including 22 male and 22 female patients. The average length of follow-up for both groups was 12 months.

The incidence of diseases for the etiology of CKD was 40.9% for diabetes mellitus and 45.4% for hypertension in the HGB level 10-12 g/dL group and was 40.9% for diabetes mellitus and 47.7% for hypertension in the HGB>12 group (Table 2).

GFR levels of both groups were noted at the first, second, third and visits. Repeated variance analyses were used to show any statistical difference between the GFR level of both groups according to the HGB level (Table 3).

These results revealed no significant difference between the first, second, third and fourth visits GFR findings (F=1.242, p>0.05).

GFR results of the patients' first, second, third and fourth visits showed no difference between the two groups (Figure 1). (F=1.892, p>0.05). Maintenance of HGB level around 10-12 g/dL or above had no statistically significant effect on patient GFR.

Table 1. Sex and HGB

		Hemoglobin level		Total
		HGB >12	HGB ≤12	
Sex	Male	22	22	44
	Female	22	22	44
	Total	44	44	88

Table 2. CKD Etiology-HGB Distribution

		Hemoglobin level		Total
		HGB >12	HGB ≤12	
CKD Etiology	DM	18	18	36
	HT	21	20	41
	PKD	2	0	2
	FSGS	0	1	1
	SLE	0	1	1
	SOLITARY KIDNEY	0	1	1
	VUR	0	1	1
	NEPHROLYTHIASIS	1	1	2
	AMILOIDOSIS	1	1	2
	WEGENER GRAN	1	0	1
	Total	44	44	88

DM: Diabetes Mellitus, HT: Hypertension, PKD: Polycystic Kidney Disease, FSGS: Focal Segmental Glomerulosclerosis, SLE: Systemic Lupus Erythematosus, VUR: Veziko Ureteral Reflux

Table 3. Beginning GFR-HGB Distribution

Visit	Hemoglobin Level	Mean	Standard Deviation	n	F Visit	p	F Visit*HGB Group	P
	HGB>12	34.7727	8.39951	44				
MDRD_GFR 1	HGB≤12	34.5455	6.98987	44				
	Total	34.6591	7.68322	88				
	HGB>12	35.8636	8.07117	44				
MDRD_GFR 2	HGB≤12	33.0773	7.25858	44				
	Total	34.4705	7.75896	88				
	HGB>12	37.3182	9.71159	44	1.242	.295	1.892	.137
MDRD_GFR 3	HGB≤12	33.8409	6.53518	44				
	Total	35.5795	8.41320	88				
	HGB>12	35.4091	9.54139	44				
MDRD_GFR 4	HGB≤12	33.6182	7.48444	44				
	Total	34.5136	8.57283	88				

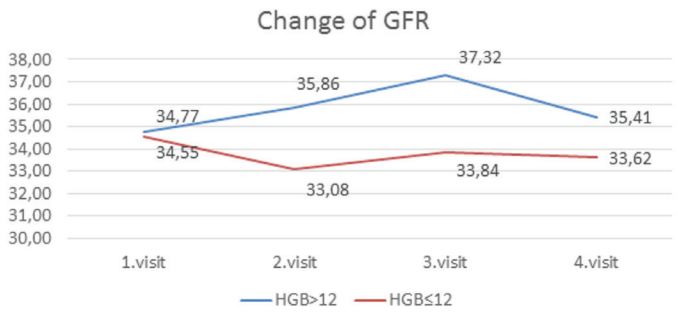

Figure 1. HGB-GFR Variance

DISCUSSION

GFR results of the patients' first, second, third and fourth visits showed no difference between the two groups (Figure). (F=1.892, p>0.05). Maintenance of HGB level around 10-12 g/dL or above had no statistically significant effect on patient GFR.

Research on the relationship between HGB level and CKD has generally been focused on the effect of EPO on disease progression and mostly focused on the relationship between mortality-morbidity and rising HGB level with EPO treatment (CHOIR-TREAT, CREAT). There are a limited number of studies comparing HGB level and GFR progression. Also, in our study the cut-off value for starting EPO treatment was 10 g/dl, increasing the importance of our research.

There was no statistical difference between the groups in patients' systolic and diastolic blood pressure, creatinine, uric acid, albumin, PTH, calcium, glucose level, and proteinuria. In this way, the rate of CKD progression in our groups was minimally affected by conditions other than HGB.

Decreased kidney function is associated with a lower hemoglobin level and a higher prevalence and severity of anemia below an estimated GFR of 60 mL/min per 1.73 m2 (6). Decreased production of EPO from the kidney in CKD patients causes normochromic normocytic anemia. Also, reduced the lifespan of erythrocytes due to uremic toxins and gastrointestinal absorption of iron causes anemia (8). According to KDIGO 2012, annual HGB level control is recommended for stage 3 CKD patients and bi-annual HGB control is recommended for stage 3-4 CKD patients (9).

Anemia is related to aggravated symptoms for CKD patients. There is a strong relationship with fatigue, depression, and decreased exercise tolerance, dyspnea, left ventricular hypertrophy, left ventricular systolic dysfunction, extended hospitalization and increased mortality (10). Serum transferrin saturation lower than 20% and serum ferritin concentration lower than 100 ng/mL is diagnostic for iron deficiency, and treatment with oral or intravenous iron replacement is required. Serum transferrin saturation higher than 30%, serum ferritin higher than 500 ng/mL, HGB levels between 10and 11.5 g/dL and these were goal levels for all CKD patients (11).

For an adult, CKD non-dialysis patient with HGB level<10 g/dL and without iron deficiency, erythropoietin (EPO) should be used with a starting dose of 50-100 unit/kg/week. The target HGB level should be 10-12 g/Dl (7).

In a past study by Mohanram et al., 1513 patients with diabetic nephropathy were divided into four groups according to HGB level (HGB<11.3, HGB 11.3-12.5, HGB 12.6-13.8, and HGB>13.8) and followed for an average of 3.4 years. The results showed that even mild anemia, Hb <13.8 g/dL, increased the risk of progression to ESKD. HGB was an independent risk factor for the progress of nephropathy to ESKD in type 2 diabetes (12). In our study, diabetes was the leading cause of CKD (40.9%), but there was no correlation between HGB level and GFR in this population (p>0.05).

EPO has a renoprotective effect on renal injury by decreasing apoptosis, caspase activity and increasing tubular regeneration (13). Gouva et al. conducted a randomized controlled trial of early versus deferred initiation of EPO in 88 non-diabetic pre-dialysis patients with serum creatinine 2 to 6 mg/dL and HGB 9 to 11.6 g/

dL. Early start of EPO in pre-dialysis patients with non-severe anemia significantly slowed the progression of renal disease and delayed the start of renal replacement therapy (p=0.012) (14). Our study had two groups (hemoglobin levels between 10 and 12 and higher than 12). Patients with unstable HGB level, outside the group limits, were excluded from the study and we did not perform any mortality and morbidity analysis. We, therefore, analyzed the hemoglobin level and the relationship to GFR without external factor bias.

Eighty-three patients with chronic kidney disease and deep anemia were divided into two groups after two months of stabilization. Epoetin was given to 43 patients, and 40 patients were selected as the control group. In the evaluation made after 48 weeks follow-up; GFR progression in the epoetin group was three times slower than the control group (15).

Seventy-three patients with chronic kidney disease and deep anemia, after eight weeks of stabilization period, 42 patients were given epoetin treatment, and 31 patients were not treated. After 36 weeks of follow-up, the creatinine level was doubled 52% in the epoetin group and 90% in the control group (p<0.0005). During follow-up, dialysis had to be initiated in 64% of the control group and 33% of the epoetin group (p <0.0005) (16).

The CHOIR study investigated 1432 patients with CKD, 715 of whom were randomly assigned to receive a dose of EPO targeted to achieve a hemoglobin level of 13.5 g/dL, and 717 of whom were assigned to receive a dose aimed to reach a level of 11.3 g/dL. The median study duration was 16 months. The main result of the study was that the improvement in the quality of life was similar in the two groups (17).

In the TREAT study involving 4038 patients with diabetes, CKD, and anemia, 2012 patients were randomly assigned to EPO to achieve HGB level of approximately 13 g/dL and 2026 patients to placebo, with rescue EPO when the HGB level was less than 9.0 g/dL. According to the results of this study, there were no overall significant differences in the rates of death, heart failure, myocardial infarction, admission for myocardial ischemia, or ESKD (18).

The CREAT study randomly assigned 603 patients with an estimated GFR of 15.0 to 35.0 ml/min/1.73 m2 of body surface area and mild-to-moderate anemia (HGB level, 11.0 to 12.5 g/dL) to a target HGB value in the normal range (13.0 to 15.0 g/dL, group 1) or the subnormal range (10.5 to 11.5 g/dL, group 2). Subcutaneous EPO was initiated at randomization (group 1) or only after the HGB level fell below 10.5 g/dL (group 2). The study findings indicate that the early complete correction of anemia does not reduce the risk of cardiovascular events and the decrease in estimated GFR over time did not differ significantly (19).

CONCLUSION

We found similar results as in previously performed studies that maintenance of HGB level between 10-12 g/dL had a similar effect on GFR impairment as compared with patients having HGB level above 12 g/dL. During the follow-up, the HGB level above 10 mg/dL is sufficient for controlling CKD progression. On the other hand, the small number of patients and short follow-up period were the limitations of our study. To understand the relationship between hemoglobin level and CKD progression, we need multicentered, prospective and large-scale clinical studies.

Ali Riza Caliskan ORCID:0000-0003-3187-8548
Yasin Sahinturk ORCID:0000-0003-4907-0766
Aygul Ozdemir ORCID:0000-0002-2961-3092
Metin Sarikaya ORCID: 0000-0002-4939-6486

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