

## Association between diabetic retinopathy and hemoglobin level

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### Abstract

**Background:** Anemia may be considered to be an independent risk factor for the development of diabetic retinopathy (DR) in patients with renal failure. The purpose of this study was to investigate the association between blood hemoglobin level and retinopathy in diabetic patients with normal renal function tests.

**Methods:** From 2009 to 2011, 1100 diabetic patients underwent retinal examination. Among them, 159 subjects were diagnosed to have DR and were compared with 318 diabetic subjects with normal retinal examination as the control group. The level of hemoglobin (Hb), Hb A1C, serum iron, ferritin, and total iron binding capacity were compared between these two groups.

**Results:** Among the 159 patients with DR, 112 (70.4%) had mild to moderate non-proliferative retinopathy (NPDR) and 47 (29.6%) had advanced retinopathy (severe NPDR or proliferative). The mean hemoglobin level in case and control group was  $12.15 \pm 1.50$  and  $12.73 \pm 1.38$  g/dl, respectively ( $p < 0.001$ ). Anemia was seen in 45.9% and 26.1% in the case and the control groups, respectively ( $p < 0.001$ ). Ferritin  $< 15$  ng/ml was seen in 7.4% and 6.1% of patients with and without DR, respectively ( $p = 0.8$ ).

**Conclusion:** The results show that diabetic patients with retinopathy have lower level of hemoglobin and higher frequency of anemia. It is suggested that the level of hemoglobin should be evaluated periodically in diabetic patients.

**Keywords:** Anemia, Diabetic retinopathy, Hemoglobin, Retinopathy

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**R**etinopathy is the major cause of morbidity in patients with diabetes and is increasing globally, with the total number of people with DM it is expected to reach to 300 million in the year 2025 (1, 2). Meanwhile, improvements of healthcare and specific treatments have increased the life expectancy and survival rate of the diabetic patients. Increased life expectancy is associated with higher prevalence of DM complications and lower life quality of the patients. One of the most important DM complications is diabetic retinopathy (DR). Various factors are associated with the development and severity of DR including high blood pressure, proteinuria, duration of DM, administration of insulin and renal disease (3). Anemia is suggested as another long term complication of DM and defined as hemoglobin level less than 13 g/dl in men and 12g/dl in women (4, 5). The prevalence of anemia in DM patients is reported as 14-48% (6-8). Anemia is supposed to be an independent risk factor for the development and progression of cardiovascular complications and heart failure chronic renal disease and DR in DM patients (9-18). In DM patients, with any amount of glomerular filtration compared to non-DM patients with the same renal function, anemia is more prevalent and more severe (6, 14, 19-20). High glycosylated hemoglobin, diabetic neuropathy, low serum albumin, younger age and also low hematocrit were reported as risk factors for the development of more severe form of DR (high risk proliferative DR) and visual loss.

Because the early diagnosis and treatment of anemia might decelerate the progression of DR, we designed this study to evaluate the association of diabetes retinopathy and blood hemoglobin level in diabetic patients without significant renal dysfunction.

## Methods

One thousand one hundred type 2 diabetic patients were entered in to this study between 2009 and 2011 in Sari, Iran. The patients with history of malignancy, gastrointestinal bleeding during the past three months, undergo treatment for anemia during the past months (receiving iron products, folic acid or vitamin B12), creatinine  $>2$  mg/dl, and pregnant or lactating women were excluded from the study. Basic data such as age, sex, duration of DM, history of hyperlipidemia, their medications along with their blood pressure was entered in the questionnaire. All patients underwent ophthalmologic examination by indirect ophthalmoscopy and the patients were divided into three groups: normal retinal examination, mild to moderate no proliferative retinopathy (NPDR) and advanced retinopathy (severe NPDR and proliferative). Retinal photography and angiography were performed in patients with severe retinopathy.

Among the 1100 referral patients, 159 subjects with DR as the case group were compared with 318 normal retinal subjects as the control group. After twelve hours of fasting, blood sampling was taken in all patients. Two milliliters citrated blood for complete blood count and 10 milliliters clotted blood for measuring hemoglobin A1C (HbA1c), serum iron, ferritin, and total iron binding capacity (TIBC) were collected and sent to the laboratory. According to the World Health Organization (WHO) definition, a hemoglobin level  $<13$  g/dL in men and  $<12$  g/dL in women were used to define anemia (5). The study was approved by Mazandaran University of Medical Sciences Ethics Committee.

The data were collected and analyzed. The data were collected and analyzed t-test used for the comparison of quantitative and chi-square for the comparison of qualitative variables between the two groups. Statistical significance was recognized at  $p<0.05$ .

## Results

The mean age of the case group was  $57.4\pm 9$  and in the control group was  $56.9\pm 9.8$  years. The other characteristics

of the patients in these two groups are shown in table 1. The mean hemoglobin level was  $12.15\pm 1.50$  g/dl in the case group and  $12.73\pm 1.38$  g/dl in the control group ( $p<0.001$ ). Serum irons, TIBC, transferrin saturation were not statistically significant between the case and control groups (table 2). The mean hemoglobin level in patients without DR ( $12.73\pm 1.38$  g/dl) was significantly higher than the patients with mild to moderate NPDR ( $12.25\pm 1.38$ ) and advanced retinopathy ( $11.89\pm 1.76$ ) ( $p=0.007$  and  $0.001$ , respectively). Anemia was seen in 45.9% in the case group and in 26.1% in the control group (OR=2.40; 95% CI: 1.61-3.58;  $p<0.001$ ).

**Table 1. Basic variables data in diabetic patients with and without retinopathy**

Variable	Diabetes retinopathy		Pvalue
	+	-	
Age (year)	57.4±9	56.94±9.80	0.6
Duration of DM (year)	10.83±6.53	10.32±6.20	0.4
Creatinine (mg/dl)	0.90±0.23	0.89±0.16	0.8
Hemoglobin A1C (%)	8.21±1.69	8.14±1.60	0.7
Dyslipidemia (%)	82.5	78.2	0.5
Hypertension (%)	61.4	53.1	0.1

**Table 2. Hematologic variables data in diabetic patients with and without retinopathy**

Variable	Diabetes retinopathy		Pvalue
	+	-	
Hb (gr/dl)	12.15±1.50	12.73±1.38	0.001
RBCcount (million/ $\mu$ L)	4.58±0.64	4.59±0.52	0.9
MCV (fL)	72.25±26.58	81.15±16.35	0.000
Iron ( $\mu$ g/dl)	75.37±25.43	76.24±30.31	0.9
TIBC ( $\mu$ g/dl)	348.94±61.94	356.77±48.35	0.4
Transferrin saturation (%)	23.16±9.86	22.01±9.01	0.5

Anemia in patients with and without DR, mild to moderate DR and advanced DR were seen in 26%, 43% and 53% cases, respectively. Ferritin  $<15$ ng/ml was seen in 7.4% and 6.1% cases with and without DR respectively ( $p=0.8$ ). There was neither statistically significant correlation between the administration of oral hypoglycemic agents (glybenclamid, metformin, acarbose and glitazone) and the

frequency or severity of DR nor the significant difference between administration of angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin receptor blockers (ARBs) and aspirin between the case and control groups. The administration of insulin was higher in the case group compared to the controls (20.5% vs 11%;  $p=0.01$ ). Hemoglobin level was similar in patients under treatment with insulin and those who did not receive ( $12.35\pm 1.68$  versus  $12.59\pm 1.36$ ,  $p=0.21$ ).

## Discussion

In this study, the level of hemoglobin in DM patients with DR was lower than those without DR. The prevalence of anemia was higher in patients with more advanced DR. Concerning the exclusion of patients with creatinine more than 2 mg/dl in our study, lower hemoglobin level in patients with DR compared to patients without DR could be unrelated to anemia due to diabetic renal failure.

Qiao et al. in Finland on 1691 DM patients found that the DM patients with hemoglobin level lower than 12 mg/dl were two times more likely to develop DR (4). Consistently, we found that anemic DM patients were 2.4 times more likely to develop DR. Davis et al. reported that low hematocrit is a risk factor of development and advanced DR (17). The etiology and pathogenesis of anemia in DM patients is multifactorial. Decreased erythropoietin production is an important cause of development of anemia in DM patients (17). Chronic hyperglycemia is involved in the pathogenesis of anemia by means of creating abnormalities in RBCs, oxidative stress, autonomic neuropathy and renal sympathetic denervation. These conditions put the renal interstitium in a hypoxic state and consequently, the production of erythropoietin by peritubular fibroblasts is impaired (17). The other possible causes of anemia include functional erythropoietin deficiency, diabetic nephropathy, chronic inflammation, high levels of ultimate glycosylated products, iron deficiency, anti-DM drugs and low testosterone levels suggested by others (21). Regarding the effect of anemia on DR, it seems that anemia-induced hypoxia leads to the increased release of vaso-proliferative factors (X factor) and bring about the progression of DR (4). Preceding studies reported that the flexibility of RBCs in DM patients is much less compared to normal individuals and this may be involved in the exacerbation of diabetic microangiopathy (21-23).

Conway et al. studied 426 DM patients for 17 years and reported a direct relationship between hemoglobin level and the development and deterioration of proliferative DR and concluded that the level of hemoglobin was a predictive factor for the development of proliferative DR in type 1 DM patients (18).

Our study did not demonstrate any relationship between the administration of hypoglycemic agents or anti-hypertensive drugs and DR, but insulin administration was significantly higher in patients with DR compared to patients without DR (20.5% versus 11.0%,  $p=0.01$ ). The limitation of our study was that we did not measure the level of testosterone in males, though the 87.4% of our patients were women.

In conclusion, our findings suggest that anemia is related to the development of DR and can be deemed as a risk factor for the deterioration of DR. Therefore, the evaluation and treatment of anemia should be a part of the follow up visits of DM patients. Further studies about the effect of anemia treatment on the severity of diabetes retinopathy are recommended.

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