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Anemia in patients with type 2 diabetes mellitus and its association with the microvascular complications

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***Abstract*---**Introduction: Anemia is more commonly seen in persons with diabetes than in persons without diabetes. There is high risk of microvascular and macrovascular complications in diabetes. Anemia is strongly associated with an increased risk of diabetic complications including nephropathy, retinopathy, neuropathy and heart failure. Aim of the study: To assess the correlation between anemia and the microvascular complications of diabetes mellitus. Materials and Methods: This was a prospective, cross sectional, hospital based study conducted in department of General Medicine at Government Medical College, Kottayam, over a period of one year. Two hundred consecutive cases of diabetes mellitus with anemia were studied for microvascular complications like diabetic neuropathy, nephropathy, retinopathy. Results: Total 200 patients were enrolled with 116 (58%) male and 84 (42%) female patients and male to female ratio was 1.3:1. The patient age ranged from 41 to 86 years and mean age was 60.78±9.38 years. Diabetic neuropathy was absent in 38% and present in 62%. Proliferative and nonproliferative diabetic retinopathy was seen in 18% and 53% cases respectively. Conclusion: Anemia has correlation with the microvascular complications of diabetes. With increasing duration of diabetes mellitus the hemoglobin levels fall progressively. Nonproliferative diabetic retinopathy is more commonly seen in patients with normocytic normochromic anemia. Neuropathy in diabetes is more commonly seen in patients with macrocytic anemia

and obesity is a risk factor for the development of neuropathy. Diabetic nephropathy is more commonly seen in patients with macrocytic anemia than other types of anemia.

***Keywords*---**Diabetes mellitus, Anemia, Microvascular complications, Diabetic retinopathy, Diabetic neuropathy, Diabetic nephropathy.

Introduction

Anemia is more commonly seen in persons with diabetes than in persons without diabetes. The characteristic features of type 2 Diabetes mellitus are hyperglycemia, insulin resistance and relative reduction in insulin secretion. The pathogenesis of diabetes mellitus is multifactorial and heterogeneous and has both genetic and environmental elements. In recent times the prevalence is seeing upward trend attributable to obesity and sedentary lifestyle and other various factors. [1] Insulin resistance and relative insulin deficiency, or a combination of both leads to type 2 diabetes [2] Diabetes is a global disease and India is no exception.

Anemia is strongly associated with an increased risk of diabetic complications including nephropathy, retinopathy, neuropathy and heart failure. It is well known that diabetes has a higher risk of microvascular and macrovascular complications. Anemia is commonly seen in patients with diabetes. The development and progression of microvascular and macrovascular complications in diabetes is associated with anemia. Anemia can falsely lead to low HbA1c levels, which in turn leads to under treatment of hyperglycemia, that further enables the progression of both microvascular and macrovascular diabetic complications. [3] Anemia can be considered as a marker of kidney damage, and anemia in diabetics has increased risk of mortality. To improve performance and quality of life of diabetics, the anemia has to be treated.

The relevance of the study is that anemia and diabetes are both common in general population and microvascular complications are associated with anemia. So early identification and correction of anemia in diabetes can delay the development of microvascular complications. In the present study, we tried to determine the correlation between anemia and the microvascular complications in diabetic patients, attending General Medicine department of our institute.

Aim of the study

To assess the correlation between anemia and the microvascular complications of diabetes mellitus

Materials and Methods

This was a prospective, cross sectional, hospital based study conducted in department of General Medicine at Government Medical College, Kottayam, over a period of one year from January 2019 to December2019. Two hundred

consecutive cases eligible for the study ie patients with diabetes mellitus and anemia attending the General Medicine department formed the study population.

Inclusion criteria:
Adult patients with diabetes mellitus and anemia based on WHO criteria

Exclusion criteria:
- Patients with chronic liver disease, chronic kidney disease stage 3,4,5 due to non diabetic causes, pregnant women, previous history of anemia, patients on treatment for anemia, patients with hematological malignancies were excluded.
- Other factors causing transient albuminuria like urinary tract infection and other acute infections were excluded.

Sample size
Required was of 164 cases based on existing prevalence and in the present study 200 cases were included.

Methodology

After getting Institutional Review Board clearance, 200 patients with Diabetes mellitus and anemia and who have consented to participate in the study were included. A study proforma was prepared and detailed history regarding symptoms, probable cause, examination and investigation findings were noted.

Clinical

examination including general examination and system examination was done. Fundus examination was done to look for diabetic retinopathy. Laboratory investigations included hemoglobin levels, mean corpuscular volume, RBC indices, platelet count and peripheral smear, renal function tests, blood sugar levels, and urine exam for albuminuria. Vibration sense, ankle jerk and Semmes Weinstein monofilament test was done to look for peripheral neuropathy. Vibration sensation was assessed using 128MHz tuning fork at the base of great toe. 5.07, 10 g Semmes Weinstein monofilament was used to assess the touch sensation. When the filament is placed on the patient's skin (usually the feet) when there is considerable loss of sensation, the patient will not be able to detect the presence of the filament at buckling.

For statistical analysis, the data was entered in Microsoft Excel and analyzed using SPSS software version 18. Quantitative variables were presented as mean and standard deviation. Categorical variables were summarized using frequency and percentage. Statistical testing of association of various factors were done using Pearson Chi square test, independent sample t test and ANOVA. p value less than 0.05 was considered as statistically significant.

Ethical consideration

The above mentioned study was conducted in this institute after obtaining the ethical clearance from the Institutional Review Board of Government Medical College, Kottayam and Department of General Medicine, Government Medical

College, Kottayam. Informed consent was obtained from all subjects who took part in the study. The privacy of the patient and confidentiality of the clinical data was maintained throughout the study. The information collected was used only for the purpose of this study. The study was done at no added cost to the patients, and did not affect the treatment given to them.

Data collection method

Diabetic patients with anemia were identified and the presence of different microvascular complications was studied. The correlation between different types of anemia and microvascular complications was identified.

Observations and Results

A total of 200 patients with diabetes mellitus and anemia were studied to determine if there is any link between anemia and microvascular complications in diabetics.

Demographic characteristics of the study population: Of the 200 patients enrolled in the study, there were 116 (58%) were male and 84 (42%) were female patients and the male to female ratio was 1.3:1. The patient age ranged from 41 to 86 years and the mean age of patients in this study was 60.78±9.38 years. Following is the age distribution: 17% of patients were between 41-50 years, 39.5% patients between 51-60 years, 27% patients between 61-70 years, 15% patients between 71-80 years and 1.5% patients were more than 80 years

BMI of the study population: Among the study population, the BMI of 51.5% patients was between 18.5-22.9, 39.5% of patients between 23-24.9 and 9% of patients more than 25.

Percentage of patients with blurring of vision: Among the 200 patients enrolled in the study, 42% gives history of blurring of vision and 58% doesn't have blurring of vision.

Distribution based on frothing of urine: Among the 200 patients enrolled for the study, 28% had frothing of urine and 72% didn't have frothing of urine.

Distribution based on symptoms of peripheral neuropathy: Among the 200 patients enrolled for the study, 30% had symptoms of peripheral neuropathy and 70% didn't have on symptoms of peripheral neuropathy.

Distribution based on duration of detected diabetes in years: Among the 200 patients enrolled in the study, 127 (63.5%) patients had detected duration of diabetes more than 5 years, (73) 36.5% patients had detected duration less than 5 years.

Distribution based on treatment of diabetes mellitus

Among the 200 patients enrolled for the study, 41.5% were on oral hypoglycemic agents, 10.5% were on insulin and 48% were on both OHA and insulin.

Distribution based on detected duration of diabetes and treatment modality: Among the study population with duration of detected diabetes less than 5 years, 87.5% were on OHA and 12.5% were on insulin containing regimen. Among the patients with duration of detected diabetes more than 5 years 62.5% were on OHA and 37.5% were on insulin containing regimen.

Distribution based on dietary habits of population: Among the 200 patients enrolled for the study 20% was vegetarian and 80% was taking mixed diet.

Distribution of Diabetic retinopathy: Among the 200 patients enrolled in the study, 18% had PDR, 53% had NPDR and the fundus examination of 29% was normal.

Distribution of vibration sensation: Among the 200 patients enrolled in the study, vibration sensation was present in 38% of patients and absent in 62%.

Distribution of ankle jerk: Among the 200 patients enrolled the study, ankle jerk was present in 68% and absent in 32 %.

Distribution of monofilament test: Among the 200 patients enrolled in the study, monofilament test was positive in 49% and negative in 51%.

Distribution of diabetic neuropathy: Among the 200 patients enrolled for the study, diabetic neuropathy was absent in 38% and present in 62%.

Distribution of hemoglobin levels in the population: Among the 200 patients enrolled for the study, the hemoglobin level was more than 11g/dL in 54% of patients, between 9.5g/dL to 10.9g/dL in 29.5%, between 8g/dL to 9.4g/dL in 16% and less than 7.9g/dL in 0.5%.

Distribution of anemia among males: Among the male population, 60.7% had hemoglobin between 13g/dL and 11g/dL.28.2% had hemoglobin between 9.5g/dL and 10.9g/dL.10.3% had hemoglobin between 8-9.4g/dL and 0.9% had hemoglobin less than 7.9g/dL.

Distribution of anemia among females: Among the female population 44.6% had haemoglobin between 12g/dL and 11g/dL.31.3% had haemoglobin between 9.5 and 10.9 g/dL.24.1% had haemoglobin between 8 and 9.4g/dL.

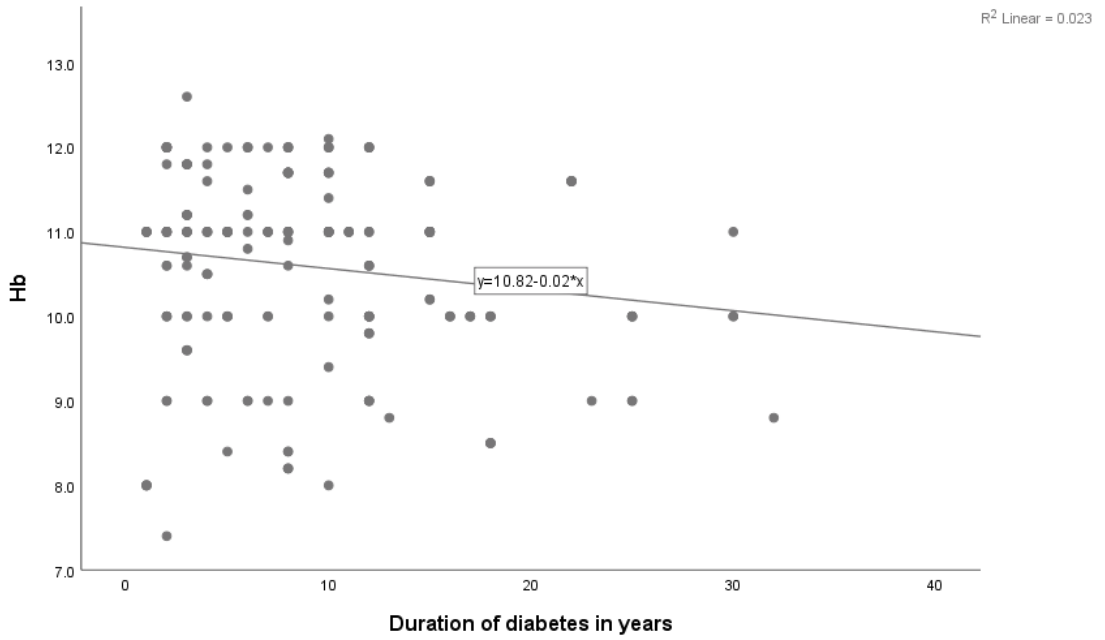

Figure 1 Scatter plot showing correlation between duration of detected diabetes and haemoglobin levels

Among the study population it was found that as the duration of diabetes increases the haemoglobin levels fall.

Distribution of MCV in the study population: Among the 200 patients enrolled, MCV was more than 100 in 15.5%, between 80 to 100 in 51% and less than 80 in 33.5%.

Distribution of peripheral smear results in the study population: Among the 200 patients enrolled for the study, 49% had normocytic normochromic anemia, 30.5% had microcytic hypochromic anemia and 20.5% had macrocytic anemia.

Distribution of serum creatinine levels in the population: Among the 200 patients enrolled for the study, serum creatinine levels was more than 1.2mg/dL in 38% and less than 1.2mg/dL in 62%.

Distribution of significant albuminuria in the study population: Among the 200 patients enrolled for the study, significant albuminuria was present in 78% and absent in 22% cases.

Distribution of Diabetic nephropathy in the study population: Among the 200 patients enrolled for the study**,** diabetic nephropathy was present in 78% and absent in 22%.

Demographic factors associated with Diabetic retinopathy

Table 1 Demographic factors associated with diabetic retinopathy

Variable	Diabetic retinopathy			P value
	PDR	NPDR	Normal	
Age				
Mean(SD)	68.11±10.48	62.01±8.25	53.97±5.49	<0.001*
Sex				
Male	21(17.9)	62(53)	34(29.1)	1.00
Female	15(18.1)	44(53)	24(28.9)	
BMI				
Mean	23.25±1.87	22.73±1.53	23.20±1.40	0.087

PDR, NPDR: Proliferative and Non-proliferative diabetic retinopathy

Among the demographic factors, patients with age group between 47 and 89 years had high risk of PDR, with a p value of 0.001 (statistically significant). Sex and BMI was not important in the development of Diabetic retinopathy

Duration of detected diabetes and relation with retinopathy

Among the 200 patients enrolled in the study, 127 (63.5%) patients had diabetes for more than 5 years, and 73 (36.5%) patients had detected duration of less than 5 years. In the former category, there were zero cases of proliferative diabetic retinopathy (PDR), 27 (37%) cases of nonproliferative diabetic retinopathy (NPDR) and 46 (63%) were normal. In the latter category, there were 36 (28.3%) cases PDR, 79(62.2%) cases of NPDR and only 12 (9.4%) cases were normal. The p value was 0.001 which was significant.

Table 2 Hemogram and relation with retinopathy

Hb	**PDR**	**NPDR**	**NORMAL**	P value
>11	6(5.6)	69(63.9)	33(30.6)	<0.001*
9.5-10.9	20(33.9)	24(40.7)	15(25.4)	
8-9.4	10(31.2)	30(40.6)	9(28.1)	
<7.9	0	0	1(100)	
MCV				
>100	12(38.7)	16(51.6)	3(9.7)	<0.001*
80-100	15(14.7)	62(60.8)	25(24.5)	
<80	9(13.4)	28(41.8)	30(44.8)	

Among the patients with diabetic retinopathy, 63.9% of patients with NPDR had a hemoglobin concentration of more than 11 g/dL. Of the patients with PDR, 33.9% had hemoglobin between 9.5 to 10.9g/dL. Also 60.8% of patients with NPDR had MCV between 80-100.Among the patients with PDR 38.7% had MCV more than 100. So NPDR was more commonly seen in patients with normocytic normochromic anemia than other types of anemia.

Distribution of Diabetic retinopathy in different types of anemia

Among the patients with normocytic normochromic anemia, 10 (10.2%) had PDR and 59 (60.2%) had NPDR. Among the patients with microcytic hypochromic anemia, 8 (13.1%) had PDR and 28 (45.9%) had NPDR. Among the patients with macrocytic anemia, 18 (43.9%) had PDR and 19 (46.3%) had NPDR. The p value was <0.001.

Table 3 Demographic factors and relation with diabetic neuropathy

Variable	Diabetic neuropathy		P value
	Present	Absent	
Age			
Mean(SD)	63.33±10.01	56.61±6.37	<0.001*
Sex			
Male	72(61.5)	45(38.5)	0.991
Female	52(62.7)	31(37.3)	
BMI			
Mean	22.87±1.69	23.11±1.36	0.029*

Based on the age distribution, patients between the age of 43.31 years and 83.35 years had diabetic neuropathy, with a significant p value of less than 0.001. No difference was noted among males and females with diabetic neuropathy (p value-0.991, statistically insignificant). Diabetic neuropathy was significantly associated with body mass index with a p value of 0.029.

Table 4 Hemogram and relation with neuropathy

Hb	Neuropathy present	Neuropathy absent	p value
>11	53(49.1)	55(50.9)	<0.001*
9.5-10.9	48(81.4)	11(18.6)	
8-9.4	23(71.9)	9(28.1)	
<7.9	0	1(100)	
MCV			
>100	27(87.1)	4(12.9)	<0.001*
80-100	52(51)	50(49)	
<80	45(67.2)	22(32.8)	

Among the patients with diabetic neuropathy, 81.4 % had hemoglobin between 9.5g/dL to 10.9g/dL and 71.9% had hemoglobin between 8g/dL to 9.4g/dL with a p-value of less than 0.001. Also 87.1% of patients with diabetic neuropathy had macrocytic anemia and 67.2% had microcytic anemia. The p value was less than 0.001 which was statistically significant.

Distribution of Diabetic neuropathy in different types of anemia on peripheral smear findings

Among the patients with normocytic normochromic anemia, diabetic neuropathy was present in 46 (46.9%) cases and absent in 52 (53.1%) cases. Among the patients with microcytic hypochromic anemia, neuropathy was present in 44 (72.1%) cases and absent in 17 (27.9%) cases. Among the patients with macrocytic anemia, diabetic neuropathy was present in 34 (82.9% cases and absent in 7 (17.1%) cases. So neuropathy in diabetes was more commonly seen in patients with macrocytic anemia than other types of anemia.

Table 5 Demographic factors and relation with diabetic nephropathy

Variable	Diabetic nephropathy		P value
	Present	Absent	
Age			
Mean(SD)	62.71±9.52	53.93±4.33	<0.001*
Sex			
Male	89(76.1)	28(23.9)	0.542
Female	67(80.7)	16(19.3)	
BMI			
Mean	22.94±1.58	23.02±1.57	0.758

Among those with nephropathy, patients between the age group of 43.67 years to 81.75 years were mostly affected with a p value of less than 0.001(statistically significant). No relation was seen between gender of the patients and BMI to diabetic nephropathy.

Duration of detected diabetes and relation with nephropathy

Among those with diabetic nephropathy, the detected duration of diabetes was more than 5 years in 119 (93.7%) cases and was absent in 8 (6.3%) cases and was statistically significant with a p value of less than 0.001. For those with

duration of less than 5 years of diabetes, nephropathy was present in 37 (50.7%) cases and absent in 36 (49.3%) cases.

Table 6 Hemogram and relation with nephropathy

Hb	Nephropathy present	Nephropathy absent	P value
>11	78(72.2)	30(27.8)	0.023*
9.5-10.9	49(83.1)	10(16.9)	
8-9.4	29(90.6)	3(9.4)	
<7.9	0	1(100)	
MCV			
>100	30(96.8)	1(3.2)	0.002*
80-100	80(78.4)	22(21.6)	
<80	46(68.7)	21(31.3)	

A total of 29 (90.6%) of patients with nephropathy had hemoglobin between 8 to 9.4, and 49 (83.1%) had hemoglobin between 9.5 to 10.9g/dL and 78 (72.2%) had hemoglobin more than 11g/dL which was statistically significant (p value less than 0.001). Also 30 (96.8%) of patients with nephropathy had MCV more than 100, and 80 (78.4%) cases had MCV between 80-100 and 46 (68.7%) had MCV less than 80 with a p value of less than 0.001.

Distribution of diabetic nephropathy in different types of anemia

Among the patients with normocytic normochromic anemia, diabetic nephropathy was present in 72 (73.5%) cases and absent in 26 (26.5%) cases. Among the patients with microcytic hypochromic anemia nephropathy was present in 45 (73.8%) cases and absent in 16 (26.2%) cases. Among the patients with macrocytic anemia, 39 (95.1%) had nephropathy and 2 (4.9%) didn't have nephropathy. P value was 0.012. So, diabetic nephropathy was more commonly seen in patients with macrocytic anemia than other types of anemia.

Discussion

In this cross sectional study, all the 200 patients were subjected to detailed history taking, examination and laboratory investigations. The mean age of patients in this study was 60.78±9.38 years. The maximum number of patients was in the age group of 51-60 years, which is 39.5% of cases and the next highest

number of patients were in the age group of 61-70 years (27%). Males contributed to 58% of the study population. In the study conducted by Rani et al [4] the mean age of the population was 56.32+ 10.02 years and 53.0% were men. In this study, microvascular complications were equally seen in both males and females, which was consistent with the study conducted by Rani et al. [4]In this study it was found that as duration of diabetes increases the hemoglobin levels fall which was consistent with the study conducted by Hosseini MS etal [5]. Normocytic normochromic anemia was the most frequent type of anemia in this study (49%), which was consistent with the study conducted by Hosseini MS et al [5]. In this study, nephropathy was seen in 78%, retinopathy was seen in 71% and neuropathy in 62%. So nephropathy was the most common microvascular complication in this study which was consistent with the study conducted by Hosseini MS et al. [5] When the demographic factors of the study population are compared, patients between the age group of 47 to 89 years had high risk of PDR with a p value of less than 0.001. Among the study population, 71% had diabetic retinopathy with 18% having PDR and 53% having NPDR. Among the 200 patients, 62% with detected duration of diabetes more than 5 years had NPDR. Among the patients with NPDR, 63.9% had hemoglobin less than 13g/dL and more than 11g/dL in males and less than 12g/dL and more than 11g/dL in females. Among patients with PDR, 33.9% had hemoglobin between 9.5 to 10.9 g/dL. NPDR was more commonly seen in patients with normocytic normochromic anemia than other types of anemia. In the study conducted by Hosseini MS et al [5], retinopathy was equally seen in patients with normocytic and microcytic anemia, the difference was observed may be because of the differences in sampling techniques. In the study conducted by Mohan et al [6], diabetic retinopathy is seen in 43% of patients. It was found that with increasing duration of diabetes and fall in haemoglobin levels there is high chance of developing diabetic retinopathy which was consistent with the study conducted by Mohan et al. [6] Among the patients between 25 and 74 years of age, diabetic retinopathy is one of the major cause for the development of impaired vision worldwide. [7] When diabetic neuropathy is taken into consideration, neuropathy was most commonly seen in patients between the age group of 43.31 to 83.33 years which was statistically significant (p value of less than 0.00).81.4% of patients with neuropathy had hemoglobin between 9.5 to 10.9 g/dL and 71.9% had hemoglobin between 8 to 9.4 g/dL (p value less than 0.001).Neuropathy in diabetes was more commonly seen in patients with macrocytic anemia than other types. In the study conducted by Hosseini MS etal [5], neuropathy was more commonly seen in patients with normocytic anemia. In the study conducted by Smith et al [8] patients with diabetic neuropathy had longer duration of diabetes and obesity is a risk factor for the development of diabetic neuropathy. In this study also it was found that high BMI is a risk factor for the development of neuropathy. Presence of significant albuminuria was considered as diabetic nephropathy. Patients with diabetic nephropathy were between the age group of 43.67 to 81.75 years which was statistically significant. The detected duration of diabetes was more than 5 years in 93.7% of patients with diabetic nephropathy (p value less than 0.001).It suggests that as the duration of diabetes increases, the chance of developing nephropathy increases.90.6% of patients with diabetic nephropathy had hemoglobin between 8 to 9.4 g/dL, 83.1% had hemoglobin between 9.5 to 10.9g/dL and 72.25 had hemoglobin more than 11 with a p value of less than 0.001. Diabetic nephropathy was more commonly seen in patients with

macrocytic anemia than other types of anemia. In the study conducted by Hosseini MS et al [5], nephropathy was more commonly seen in patients with normocytic anemia.

In the present study, no relation was seen between gender of the patients and BMI to diabetic nephropathy. Modifiable risk factors and ethnic disparity plays role in the development of diabetes mellitus. Data from the prospective Nurses' Health Study (NHS) collected over 20 years, it was found that the risk for developing diabetes in women, corrected for BMI, was increased for Asians, Hispanics, and African Americans (relative risk [RR] 2.26, 1.86, and 1.34, respectively) compared with whites. [9]

Altered glomerular hemodynamics results in activation of the renin-angiotensin aldosterone system (RAAS) and elevated glomerular filtration rate (GFR). [10] There is deposition of advanced glycosylation end products in basement membranes in diabetes due to oxidative stress and inflammation which are intimately related to each other. [11, 12]The findings of our study concur with the literature though there are some limitations in our study as follows:

Limitations of the study

The etiological factors related to anemia were not studied. Being a cross-sectional study, duration of anemia and its long term effects on diabetes mellitus couldn't be differentiated. Also, as this was a hospital based study, the results can't be applied to the general population.

Conclusion

Anemia has correlation with the microvascular complications of diabetes. With increasing duration of diabetes mellitus the hemoglobin levels fall progressively. Nonproliferative diabetic retinopathy is more commonly seen in patients with normocytic normochromic anemia. Neuropathy in diabetes is more commonly seen in patients with macrocytic anemia and obesity is a risk factor for the development of neuropathy. Diabetic nephropathy is more commonly seen in patients with macrocytic anemia than other types of anemia.

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