

**Original research article :**

## **A study of profile of anemia in patients with type 2 diabetes mellitus with normal renal function**

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### **Abstract :**

**Background and Aim:** Anemia is commonly observed in patients with diabetes mellitus and it contributes to the progression of complications both microvascular and macrovascular in patients with diabetes mellitus. The prevalence of anemia ranges from 13% to 45% in patients with DM. There are limited studies on incidence of anemia in people with diabetes mellitus with no renal impairment. The current study is mainly to study the factors contributing to the development of anemia in patients with type 2 DM with normal renal function and also to know the pattern of anemia in such patients.

**Methods:** This was a crosssectional study of 230 cases, over a period of 2 years. Type 2 DM patients with normal eGFR were chosen. Occurrence of anemia in diabetic subjects with normal renal function was assessed.. **Results:** In our study it was found that 21.73% of the diabetic subjects had anemia. 27.7% of males had anemia while 19.88% of females had anemia though males accounted for only 23.47% of the study population. Out of the 50 anemic subjects,12.6% had Iron deficiency anemia , 5.7% anemia of chronic disease .Out of all the anemic subjects most of them had mild to moderate anemia and most (76%) were asymptomatic.. **conclusion:** Anemia occurs in a significant percentage of subjects with type 2 diabetes with normal renal function. We conclude that Glycemic control and duration of diabetes do not influence Hb levels, in a significant manner.

**Keywords:** HbA1c, Anemia , Diabetes mellitus

### **Introduction:**

Diabetes mellitus is a disease marked by chronic hyperglycemia with disturbances in carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The effects of diabetes mellitus are long-term damage, dysfunction, and failure of various organs. The prevalence of type 2 diabetes has risen alarmingly in the past decade , in large part linked to the trends in obesity and sedentary lifestyle. Diabetes is among the largest global health emergencies of the 21st century<sup>1</sup> , Anemia is a commonly observed condition in patients with diabetes mellitus<sup>2</sup> and it contributes to the progression of complications both microvascular and macrovascular in patients with diabetes mellitus<sup>2</sup>.

There are number of possible mechanisms for the development of anemia in diabetes patients. Failure of the kidney to increase erythropoietin (Epo) release in response to a decreasing hemoglobin (Hb) level appears to be the key contributor to the development of anemia<sup>3</sup>.However, numerous hypotheses have been proposed including efferent denervation of the kidney due to autonomic neuropathy leading to reduced erythropoietin production, chronic renal hypoxia, tubulointerstitial disease, altered iron metabolism, drugs, hyperglycaemia and systemic inflammation<sup>4</sup>.

The prevalence of anemia ranges from 13% to 45% in patients with diabetes mellitus, depending upon the ethnicity and diagnostic criteria used<sup>2</sup> and it is especially high when associated with renal impairment<sup>5</sup>. While limited studies have reported the incidence of anemia in people with diabetes mellitus with no evidence of renal impairment.

### **Aims and Objectives of the study**

The current study is mainly to study profile of anaemia in diabetes patients with normal renal function.

### **Materials and Methods:**

Source of data:

The study was conducted on 230 patients with type 2 diabetes mellitus with normal renal function visiting different hospital attached to bangalore medical college and research institute

Method of collection of data :

Design of study: cross sectional study.

Study period :november 2017 to may 2019

Place of study :hospitals attached to bmcri, bangalore.

Sample size:

Based on previous study by rathod g b et al<sup>93</sup> 18% of patients with type 2 diabetes mellitus with normal renal function were anemic.

The sample size calculation is according to the formula

$$N = z^2 \frac{pq}{d^2}$$

Where  $z^2 = 1.96$   $P = 18$ ,  $q = 100 - 18$   $D = \text{absolute precision} = 5$

$$N = 1.96 \times 18 \times 82 / 5^2 = 226.8 \approx 227 \approx 230$$

Inclusion criteria

1. Patients aged  $\geq 18$  yrs.
2. Patients willing to give informed written consent.
3. Patients with type 2 diabetes mellitus as per ada criteria
4. Patients with normal renal function.

Exclusion criteria

1. age  $\leq 18$  years.
2. Patients with abnormal rft<sup>126</sup>
3. Patients with associated ckd (as per egfr as calculated by cockcroft-gault equation)<sup>127</sup>
4. Patients on any prolonged therapy with drugs with bone marrow suppressant actio statistical analysis used:

After obtaining ethical clearance and approval from the Institutional Ethics Committee of BMCRI, Written informed consent was taken from the patients

Data was collected by semi structured questionnaire, clinical examination and investigations].

Using study proforma data was collected and analyzed of all the patients satisfying the inclusion and exclusion criteria. Patients with type 2 diabetes mellitus with normal renal function were screened for the presence of anemia by clinical means and use of basic laboratory tests like Complete blood counts. Those with anemia were worked up further with laboratory tests as required to know the type of anemia and cause. The subjects were

also compared among themselves with regard to severity of anemia and its relation to glycemic control and duration of diabetes.

**Statistical analysis:**

Data was entered in Microsoft excel and was exported into SPSS version 21.0. Data was analyzed by descriptive statistics, student’s t test was used for significant difference between 2 means, correlation co-efficient was used for relationship between 2 variables. P value of <0.05 was considered significant.

**Observation and Results:**

Table 1: Mean age distribution of the subjects

	N	Minimum	Maximum	Mean	Std. Deviation
Age	230	24	87	54.11	12.143

The mean age of the study subjects was 54.11 ± 12.143 years in the present study.

Table 2: Gender-wise distribution of the subjects

	Frequency	Percent
Males	54	23.5
Females	176	76.5
Total	230	100.0

In the present study, females (76.5%) outnumbered males ( 23.5%).

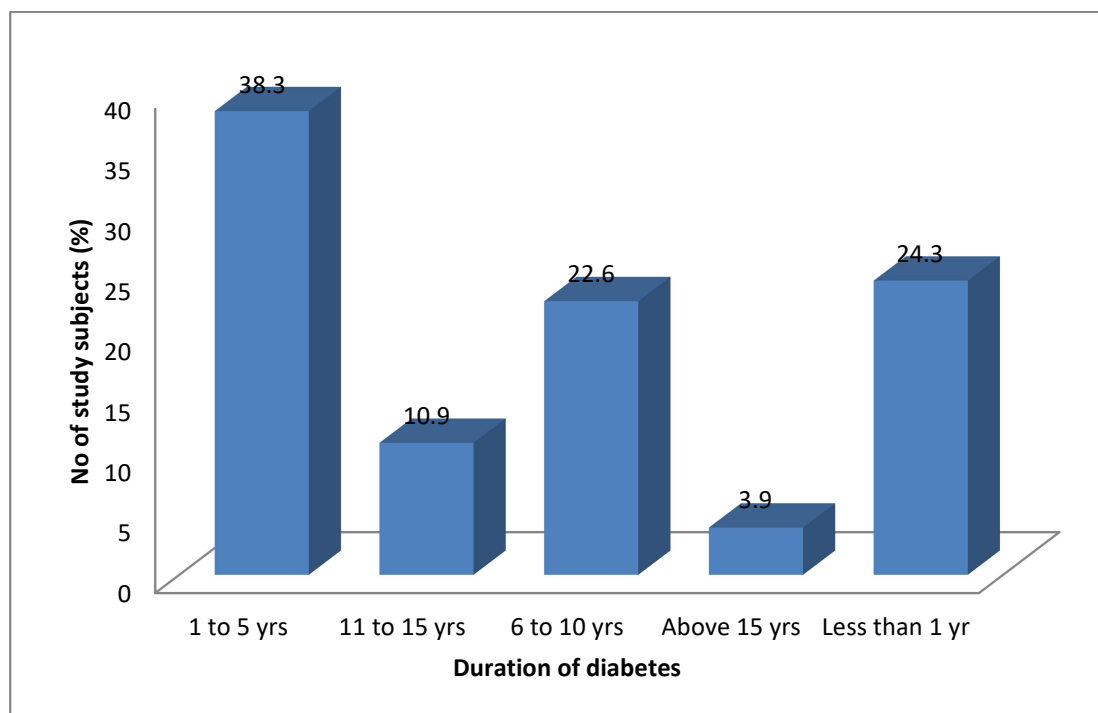


Figure 1: Distribution of the subjects based on duration of diabetes

Table 3: Distribution of the subjects based on anemia

	Frequency	Percent
No	180	78.3
Yes	50	21.7
Total	230	100.0

Anaemia was present in 21.7% of the study subjects and was absent in 78.3% of the study subjects.

Table 4: distribution of the subjects based on type of anemia

	Frequency	Percent
Iron deficiency anaemia	29	12.6
Vitamin B12 deficiency	6	2.6
Anemia of chronic disease	13	5.7
Iron and folate deficiency	1	.4
Pancytopenia	1	.4
Not anaemic	180	78.3
Total	230	100.0

Table 5: cross-tabulation of duration of diabetes and status of anaemia

Duration of diabetes		Anaemic		Total
		No	Yes	
1 to 5 yrs	Count	66	22	88
	Percent	36.7%	44.0%	38.3%
11 to 15 yrs	Count	20	5	25
	Percent	11.1%	10.0%	10.9%
6 to 10 yrs	Count	40	12	52
	Percent	22.2%	24.0%	22.6%
Above 15 yrs	Count	7	2	9
	Percent	3.9%	4.0%	3.9%
Less than 1 yr	Count	47	9	56
	Percent	26.1%	18.0%	24.3%
Total	Count	180	50	230
	Percent	100.0%	100.0%	100.0%

Chi-square value- 1.70
P value- 0.78

Table 6: pearson's correlation between duration of diabetes, hb, hba1c classified by anemic status

	No		Yes	
	R value	P value	R value	P value
Duration of Diabetes v/s Hb	0.044	0.559	-0.088	0.54
Duration of Diabetes v/s hba1c	-0.049	0.51	-0.041	0.776
Hb v/s hba1c	0.001	0.99	-0.088	0.54

Table7: pearson's correlation between duration of diabetes, hb, hba1c classified by type of anaemia

	Iron deficiency anaemia		Vitamin B12 deficiency		Anemia of chronic disease	
	R	P	R	P	R	P
Duration of Diabetes v/s Hb	-0.09	0.63	0.39	0.43	-0.31	0.29
Duration of Diabetes v/s hba1c	-0.32	0.09	0.33	0.51	0.43	0.13
Hb v/s hba1c	0.38	0.042*	0.56	0.24	-0.59	0.03*

\*significant

Table 8: distribution of the subjects based on the cause for anaemia

	Frequency	Percent
Iron deficiency anaemia	29	58.0
Vitamin B12 deficiency	6	12.0
Anaemia of chronic disease	13	26.0
Iron and folate deficiency	1	2.0
Pancytopenia	1	2.0
Total	50	100.0

Table9: distribution of the subjects based on peripheral smear

	Frequency	Percent
Microcytic	30	60.0
Macrocytic	6	12.0
Normocytic	13	26.0
Dimorphic	1	2.0
Total	50	100.0

60% of the peripheral smears showed microcytic type, followed by normocytic in 26%, macrocytic in 12% and dimorphic in 2%.

Table10:cross-tabulation of usage of metformin and anaemia

		Groups		Total
		Non-Anaemic	Anaemic	
NO	Count	7	6	13
	Percent	3.9%	12.0%	5.7%
YES	Count	173	44	217
	Percent	96.1%	88.0%	94.3%
Total	Count	180	50	230
	Percent	100.0%	100.0%	100.0%
Chi-square value- 4.82				
P value- 0.028*				

\*significant

Table11: distribution of the subjects based on evidence of malabsorption

	Frequency	Percent
None	48	96.0
Chronic diarrhea	1	2.0
H pylori infection	1	2.0
Total	50	100.0

Table12: distribution of the subjects based on alcoholism

	Frequency	Percent
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No	46	92.0
Yes	4	8.0
Total	50	100.0

Table 13: distribution of the subjects based on thyroid function

	Frequency	Percent
Normal	44	88.0
Hypothyroidism	6	12.0
Total	50	100.0

**Discussion:**

1) Sample size with Age and sex Distribution

This is a cross-sectional study of 230 cases. The mean age is 54.11±12.14 years in the study group. In a study by Rathod G B et al, mean age in study patients was 59±13 years<sup>6</sup>,

Out of the 230 subjects, 54 were males and 176 were females. However, in a study done by Rathod G B et al, in diabetic patients out of the 200 cases, 86 cases were females and 114 were males<sup>6</sup> which differed from the gender ratio of the current study which has predominant female population

2. Renal Function and normal cutoff

The subjects chosen in our study had normal renal function as per the eGFR cutoffs by KDIGO<sup>7</sup>. Also in our study subjects with age adjusted eGFR falling below the cutoffs were included as per Third National health and nutrition examination survey data<sup>8</sup> especially for the subjects aged more than 60 years. (there were 82 subjects who were above 60 years of age and out of them for 44 subjects this age adjusted cutoff was applied. Rest had their eGFR >90) As per study by C Grossman et al, the eGFR cutoff chosen was 60ml/min<sup>10</sup>. But in our study the cutoff in accordance with KDIGO was chosen as 90ml/min.

In a study by Puneeth B S et al<sup>9</sup>, Out of 100 patients 16% of them had Diabetic nephropathy.

3. Occurrence of anemia

The occurrence of anemia in a study by Rathod G B et al<sup>6</sup> on diabetic subjects was found to be 18%. In our study it was found to be 21.73%. The above said study had similar population distribution in terms of renal function. 87% of subjects in the above quoted study had normal serum creatinine. In our study all the subjects had normal renal function.

Another study by C Grossman et al<sup>10</sup> which was conducted in diabetic individuals with normal renal function, had anemia in 10.8% of subjects in a total of 445 diabetics.

In a study by Archana Gupta et al<sup>11</sup> 79 patients (79%) had haemoglobin levels below cut off of 12 g/dL for females and 13 g/dL for males. This was conducted in Jammu for a period of 6 months.

Anemia was present in 45% of patients in the study by Puneeth B S et al<sup>9</sup>.

4. Anemia

Anemia profile wasn't done in most of the studies. In our study out of the 50 anemic subjects,

12.6% had Iron deficiency anemia which was the most common form of anemia. Next being anemia of chronic disease which accounted for 5.7% .

60% had microcytic anemia, the most common form and 26% had normocytic anemia the next most common form.

Previous studies on diabetic patients have shown that longstanding poorly controlled diabetes is associated with normocytic normochromic anaemia and precedes clinical evidence of renal impairment<sup>12</sup>. Normocytic mild anaemia is a characteristic presentation of anaemia in chronic diseases and it evolves into microcytic as the severity of the anaemia increases<sup>13</sup>

Out of the 50 anemic subjects, most of them (76%) were asymptomatic. Out of the symptomatic subjects, fatigue was the most common symptom.

Considering the gender wise occurrence, 27.7% of males had anemia while 19.88% of females had anemia though males accounted for only 23.47% of the study population.

Of the anemic subjects, 16% had evidence of blood loss.

12% of the anemic subjects had associated hypothyroidism.

8% of the anemic subjects had history of significant alcohol consumption. In comparison as per study by Puneeth B S et al<sup>9</sup> 42.9% of patients with anemia were alcoholics

2 subjects out of 50 had evidence of malabsorption. One had history of chronic diarrhea and the other was detected to have H pylori infection with atrophic gastritis.

Bone marrow examination was done in one of the subject with pancytopenia which was found to be normocellular marrow.

#### 5. Effect of Glycemic control on anemia

Mean HbA1C levels in anemic subjects was 8.96 while it was 8.45 in the non anemic group. However there was no statistically significant co-relation between the 2 variables (Hb and HbA1C)

This was Similar to the study by Rathod G B et al<sup>6</sup> which concluded that Hb levels were not associated with glycaemic control as measured by HbA1C. However In the study by Archana Gupta et al<sup>11</sup>, a higher incidence of anemia was seen in patients with high blood glucose levels and poorly controlled HbA1c levels. Out of 47 male patients, 35 (74.5%) had blood glucose levels more than 130 mg/dL. This correlates with number of anemic males i.e. 31 patients (39.3%). 35 males (44.8%) had poorly controlled HbA1c levels. Out of 53 females, 43 (81%) had blood glucose levels >130 mg/dL and anemia was seen in 48 females (60.7%). 43 females (55.2%) had poorly controlled HbA1c levels.

The study conducted by Kojima. K<sup>14</sup> also showed that long standing poorly controlled diabetes was associated with anemia.

#### 6. Effect of duration of diabetes on anemia

Mean duration of diabetes in anemic subjects was 5.18±4.78 years. While in non anemic group it was 5.39±5.85 years. Majority of the study subjects had 1-5 years duration of diabetes ( 38.3%), followed by < 1 year ( 24.3%), 6-10 years ( 22.6%), 11-15 years ( 10.9%) and > 15 years ( 3.9%).

18% of anemic subjects had diabetes for less than 1 year , 44% of anemic subjects had diabetes for 1 to 5 years, 24% of anemic subjects had diabetes for 6 to 10 years, 10% of anemic subjects had diabetes for 11 to 15 years, 4% of anemic subjects had diabetes for more than 15 years. And the duration of diabetes was not found to have statistically significant co-relation with Hb levels. In contrast In the study by Puneeth B S et al<sup>9</sup> 25% of patients



with diabetes for <1 year had anemia, 51.6% had anemia who were diabetic for 1-5 years, 64% had anemia who were diabetic for 6-10 years and 33.34% had anemia who were diabetic for >10years.

In contrast, the study by Rathod G B et al<sup>6</sup> revealed out of the 36 patients of anemia with diabetes mellitus, 21 (58.33%) patients had diabetes mellitus for more than 5 years duration and individuals with duration of diabetes of more than 5 years have 1.56 times higher risk of developing anemia than those with diabetes for less than 5 years

#### 6.Role of metformin

Analysis was done to find association between usage of metformin and Hb levels. But there was no association which was statistically significant. In view of small number of subjects with B12 deficiency anemia (6 patients) association between B12 deficiency anemia and metformin use couldn't be analysed.

#### Strength of our study

- Ours is one of the first few studies investigating the occurrence of anemia in diabetics with normal renal function.
- It is also one of the first study investigating the different patterns and distribution of anemia in diabetics with normal renal function
- Our study is done to correlate Anemia(Hb levels) with Glycemic control(HbA1c) in diabetics with normal renal function.
- The limitation of our study
- Predominant female population in our study

#### Conclusion:

- Anemia occurs in a significant percentage of subjects with type 2 diabetes with normal renal function. Screening for anemia should be considered in diabetes patients who are attending out-patient clinic, as the proportion of anemia is high in T2DM. This screening should not be limited to patients with diabetic nephropathy, as it can be seen that significant proportion of anemia occurs even in patients with normal renal function. Microvascular and macrovascular complications of diabetes mellitus can be prevented by identifying anemia and its aggressive correction.
- Iron deficiency anemia was the most common form of anemia, next being anemia of chronic disease in individuals with type 2 diabetes with normal renal function.
- Mean HbA1c in anemic individuals is higher than in non-anemic, though not significant
- We conclude that Glycemic control does not influence Haemoglobin levels, in a statistically significant manner.
- Duration of diabetes also does not influence Haemoglobin levels in a statistically significant manner.
- In anemia of chronic disease in diabetic subjects, Glycemic control can influence haemoglobin levels. Good glycemic control was associated with higher Haemoglobin levels among the above subjects.
- There was no statistically significant co-relation between Hb and HbA1C and also between Hb and duration of diabetes

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