ORIGINAL ARTICLE

Prevalence of Anemia and its Types among Type 2 Diabetic Patients with Preserved Renal Functions

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Abstract

Background: Diabetes mellitus is among the most prevalent diseases of the current century. Compared to healthy people, patients suffering from Diabetic Mellitus are two to three times more likely to have anemia. Anemia found in diabetes patients is often unrecognized like many other chronic diseases. The occurrence of anemia also puts additional risk of microvascular complications among diabetic patients.

Objective: This study was conducted to determine the frequency of anemia and its types in patients with type II diabetes mellitus with preserved renal function.

Methods: A cross-sectional study was done among 366 consenting adult patients with diabetes of both genders, fulfilling the inclusion criteria attending medical OPD at PNS Rahat Hospital from January 2023 to January 2024. Demographic information and clinical history were entered using an interviewer-administered questionnaire. Aseptic condition techniques were used by trained hospital staff for blood sample collection. All included patients had normal renal function. Complete blood picture, renal function tests and HbA1c were recorded. Anemia was defined as per WHO criteria, HB level less than 13.0g/dL and in women with an HB level less than 12.0g/dL. HbA1c was used as a tool for glycemic control. The severity of anemia was assessed and co-related with glycemic control and duration of diabetes. SPSS version 27.0 was employed for data analysis.

Results: Among 366 included patients, 178 (48.6%) were female and 188 (51.4%) were male. The mean age of the patients was 59.67±8.18 years, ranged 39 to 81 years with a mean duration of diabetes 7.69±0.74years. Their mean hemoglobin level ranged from 13.33±1.87 (10.10 to 17.10) g/dl. A total of 133 patients (36.3%) were anemic. Among anemic patients 55(41.4%), 31(23.3%), and 47(35.3%) exhibited microcytic anemia, normocytic anemia, and macrocytic anemia, respectively. Of those anemic diabetic patients, 131(98.5%) had HbA1c <7% and only 2 (1.5%) did not. Also, the majority of anemic patients had a duration of disease more than 10 years.

Conclusion: Findings from the results of our study lead us to the conclusion that anemia is a serious yet undermined threat to diabetic people even without renal dysfunctions which significantly impairs the quality of life. Our results also showed that poor diabetic control, advancing age, and longer duration of illness were directly linked to the higher incidence of anemia in diabetes patients without renal insufficiency.

Keywords: *Anemia, type 2 diabetes mellitus, glycosylated hemoglobin, renal insufficiency, glycemic control.*

INTRODUCTION

Diabetes mellitus consists of an array of dysfunctions characterized by hyperglycemia and impaired metabolism of proteins, fats, and carbohydrates as a result of reduced insulin action, production, or both [1]. According to worldwide epidemiological statistics, the number of cases of diabetes has significantly increased, from 108 million in 1980 to 463 million in 2019 and is expected to reach 592 million by 2035. 4.2 million People died from diabetes and its complications in 2019. About 7% of the global population has diabetes mellitus type 2, which makes up 90-95% of all worldwide disease cases. Third-world nations especially are most affected [2, 3]. Diabetes mellitus is an important component of metabolic syndrome which includes several conditions including obesity, type 2 diabetes mellitus (T2DM), insulin resistance, elevated blood pressure, and dyslipidemia are reaching epidemic proportions. Insulin resistance, elevated blood pressure, and dyslipidemia is reaching epidemic proportions. Even in patients with preserved renal function, diabetes markedly elevates the incidence of anemia [4]. The etiology and pathophysiology of anemia in diabetes are influenced by several variables. These include low testosterone, iron insufficiency, anti-diabetic medications, diabetic neuropathy, elevated levels of advanced glycation end products, and chronic inflammation [5, 6].

Individuals with diabetes have cyanocobalamin, iron and folate, deficiencies, which can result in a variety of anemia. It suggests poor nutrition and deteriorating health [2, 7]. Due to symptoms including fatigue, pale complexion, tachycardia, headache, restlessness, chest discomfort, and numbness or coldness in the extremities, anemia in type 2 diabetes is commonly misdiagnosed. A person's quality of life can be negatively impacted by even moderate anemia, and untreated anemia can have serious negative effects on one's health. It is crucial to identify anemia in people with diabetes as

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a result. There is strong evidence that anemia raises the risk of macro- and microvascular complications connected to diabetes. It can worsen vascular, kidney, and heart issues—all of which are more prevalent in diabetes patients than in non-diabetic people [8, 9]. Prolonged hyperglycemia may cause oxidative stress, sympathetic denervation of the kidney associated with autonomic neuropathy, and decreased red blood cell deformability. These elements encourage a hypoxic environment in the renal interstitium, which affects the peritubular fibroblasts' ability to produce erythropoietin. A major factor contributing to early anemia in people with diabetes mellitus is an inappropriately low erythropoietin level [10].

It is generally known that anemia occurs in diabetes people who are experiencing renal failure. There has been relatively little research on the incidence of anemia in people with diabetes before renal dysfunction. According to current guidelines, people with Type 2 diabetes who have maintained renal function do not require routine screening for anemia. For this reason, among diabetics with normal renal function, anemia is rarely evaluated. As a result, research on the prevalence of anemia in diabetic patients before renal impairment is now crucial so we carried out this study to improve the knowledge and awareness of anemia among diabetic patients as well as to identify areas in which screening and treatment guidelines need to be changed to meet their needs and achieve better outcomes.

METHODOLOGY

It was a cross-sectional study carried out at PNS Rahat Hospital, Karachi, Pakistan among patients who visited medical and endocrine OPD from January 2023 to January 2024. Approval from ethical committee (Reference # ERC/PNR/005/2023, 30/01/2023) of the hospital was taken before conducting the study.

The sample size was calculated through Sample Size Calculator by Wan Nor Arifin (Available at: https://wnarifin.github.io/ssc/ss1prop.html) by taking the prevalence of anemia =39% [11], margin of error =5%. The total calculated sample size was 366 patients. All the patients had normal renal function tests with the duration of diabetes at least one year.

Patients with abnormal kidney functions (s. creatinine ≥ 1.2 mg/dL or proteinuria) were not included. Furthermore, patients with unstable cardiac or neurological diseases, chronic liver disease, peripheral vascular disease, recent blood loss or blood donation and hemolytic anemia as well as hemoglobinopathies and cancers were excluded.

A detailed history was taken which included the duration of diabetes and its complications, any other co-morbidities and any past medication history. Blood samples were collected with aseptic measures for serum creatinine and, complete blood analysis, glycated hemoglobin and urine analysis. Anemia was defined as per WHO for males having HB <13 mg/dl and females having HB <12 mg/dl [12]. Microcytic, normocytic and macrocytic anemia were classified based on MCV <75, >75<95, and >95 respectively. HbA1c <7.0% was taken as controlled whereas patients with HbA1c level >7.0% were categorized as uncontrolled diabetic [13].

Statistical Analysis

IBM SPSS Statistics version 27 was used for data analysis. For quantitative variables, percentages and frequencies were reported, but mean and standard deviation were computed. To compare categorical variables with anemia type, the Chi-Square test was utilized. One-way ANOVA was applied to compare numerical variables with anemia type. By using binary logistic regression, odds were determined for patients with variable with $p<0.05$ in univariate analysis were used to compute adjusted odds ratio. P-values below 0.05 were regarded as statistically significant.

RESULTS

The current study included 366 patients in total, with a mean age of 59.67±8.18 years. 51.4% of the patients were men and 48.6% were women. The values for the mean HbA1c, hemoglobin level, and duration of diabetes were 7.69±0.74%, 13.33±1.87 g/dl and 8.87±4.31 years, respectively. The majority of patients (85.6%) were older than 50 years. Out of the 366 patients, 80.3%

Table 1: Descriptive statistics of study population.

Variables	n (%)
Gender	
Male	188(51.4)
Female	178(48.6)
Age (years)	
Mean± standard deviation	59.67±8.18
Groups	
≤50 years	52(14.2)
>50 years	314(85.8)
HbA1c Level (%)	
Mean± standard deviation	7.69±0.74
Groups	
HbA1c<7 (Controlled diabetes)	72(19.7)
HbA1c≥7 (Un-controlled diabetes)	294(80.3)
Duration of diabetes (years)	
Mean± standard deviation	8.87±4.31
Groups	
≤5 years	94(25.7)
6-10 years	137(37.4)
>10 years	135(36.9)
Haemoglobin (g/dl)	
Mean± standard deviation	13.33±1.87
Groups	
Anemic	133(36.3)
Non-Anemic	233(63.7)
Anemia Type (n=133)	
Microcytic (<75)	55(41.4)
Normocytic (75-95)	31(23.3)
Macrocytic (>95)	47(35.3)

Table 2: Association and mean comparison of demographic and clinical factors according to anemia.

Variables	Anemia		p-value
	Anemic n(%)	Non-anemic n(%)	
Gender			
Male	61(45.9)	127(54.5)	0.112
Female	72(54.1)	106(45.5)	
Age (years)#	62.29±6.33	58.18±8.73	<0.001*
Age Group			
≤50 years	4(3.0)	48(20.6)	<0.001*
>50 years	129(97)	185(79.4)	
Diabetes duration (years)#	10.45±3.79	7.97±4.34	<0.001*
Duration of diabetes			
≤5 years	12(9)	82(35.2)	<0.001*
6-10 years	49(36.8)	88(37.8)	
>10 years	72(54.1)	63(27)	
Controlled diabetes			
Controlled diabetes	2(1.5)	70(30)	<0.001*
Un-controlled diabetes	131(98.5)	163(70)	

#Numerical variables expressed as mean ± standard deviation
*Significant at 0.05 levels.

had uncontrolled diabetes. A total of 133 (36.3%) of the patients in our study were found to be anemic. Among 133 anemic patients, 41.4% were microcytic, 23.3% were normocytic, and 35.3% were macrocytic. Table **1** presents comprehensive descriptive information of the study population.

Out of 133 diabetic patients with anemia in our study, the mean age and diabetes duration were 62.29±6.33 years and 10.45±3.79 years respectively. A significant association was found for age (p<<0.001) and diabetes duration (p<0.001) as presented in Table **2**.

Anemia was found to be significantly associated with age group (p<0.001), diabetes duration (p<0.001), and controlled diabetes (p<0.001). Table **2** displays the comprehensive association data for anemia.

Table **3** presents the comprehensive odds results. Through multivariate logistic regression, it was discovered that patients under 50 years old had a lower likelihood of anemia compared to those over 50 (aOR=0.288, p=0.032). Individuals who have had diabetes for less than five years are less likely to be anemic than those who have had the disease for more than ten years (OR=0.206, p<0.001. Individuals who have had diabetes for five to ten years are less likely to be anemic than those who have had the disease for more than ten years (OR=0.516, p=0.014). Patients with well-managed diabetes also have a lower incidence of anemia as compared to those with uncontrolled anemia.

Table **4** displays the comprehensive association data for the anemia type. Significant associations were discovered between the type of anemia with gender (p=<0.001) and age group (p=0.034).

Table 3: Factors associated with anemia.

Variables	Un-Adjusted		Adjusted	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Gender				
Male	0.707 (0.461-1.084)	0.112	-	-
Female	Ref			
Age Group				
≤50 years	0.120 (0.042-0.340)	<0.001*	0.288 (0.092-0.901)	0.032*
>50 years	Ref		Ref	
Duration of diabetes				
≤5 years	0.128 (0.064-0.256)	<0.001*	0.206 (0.095-0.448)	<0.001*
6-10 years	0.487 (0.300-0.792)	<0.001*	0.516 (0.305-0.873)	0.014*
>10 years	Ref		Ref	
Controlled diabetes				
Controlled diabetes	0.036 (0.009-0.148)	<0.001*	0.039 (0.009-0.163)	<0.001*
Un-controlled diabetes	Ref		Ref	

Ref: Reference category, CI: Confidence interval.
Binary logistic regression was applied.
*Significant at 0.05 levels.

Table 4: Association and mean comparison of demographic and clinical factors according to anemia type.

Variables	Anemia			p-value
	Microcytic n(%)	Normocytic n(%)	Macrocytic n(%)	
Gender				
Male	9(16.4)	21(67.7)	31(66)	<0.001*
Female	46(83.6)	10(32.3)	16(34)	
Age (years)#	62.01±4.40	61.61±9.51	63.06±5.70	0.565
Age Group				
≤50 years	0(0)	3(9.7)	1(2.1)	0.034*
>50 years	55(100)	28(90.3)	46(97.9)	
Diabetes duration (years)#	10.41±3.49	9.54±3.90	11.08±4.00	0.216
Duration of diabetes				
≤5 years	2(3.6)	5(16.1)	5(10.6)	0.156
6-10 years	24(43.6)	12(38.7)	13(27.7)	
>10 years	29(52.7)	14(45.2)	29(61.7)	
Controlled diabetes				
HbA1c<7 (Controlled diabetes)	0(0)	1(3.2)	1(2.1)	0.342
HbA1c≥7 (Un-controlled diabetes)	55(100)	30(96.8)	46(97.9)	

#Numerical variables were expressed as mean ± standard deviation
*Significant at 0.05 levels.

DISCUSSION

With about 33 million people with diabetes, Pakistan ranks 3rd among the most prevalent countries with diabetes mellitus [14]. In addition to this, Pakistan is placed at the top place for having the highest comparative diabetes prevalence rate in 2021 at 30.8%. Pakistan is also the country with the highest percentage of deaths under the age of 60 due to diabetes, with 35.5%. Most

of the affected population with this potentially lethal disease lacks knowledge of their illness and its related complications [15]. Anemia is a significant health phenomena approximately affecting about 1.74 billion (22.8%) of the global population and predominantly affects low and middle-income countries [16]. However, a global estimate of the prevalence in type 2 diabetic adult population is lacking.

The prevalence of anemia among diabetic patients is higher than normal healthy individuals and it is usually considered a complication of diabetic nephropathy. In a global systematic review and meta-analysis inculded 24 studies, the pooled prevalence of anemia was 27% [16].

we conducted this study to determine the prevalence of anemia and its profile among diabetic patients without any nephropathy since early recognition of anemia is extremely important as anemia significantly potentiates the micro and vascular diabetic complications, and its timely treatment will not only improve quality of life but will delay the onset of these complications as well.

Our study shows the prevalence of anemia to be 36.3% of patients among diabetic patients with preserved renal function, similar results were observed from another study which showed an anemia prevalence of 32.4% among diabetic persons [12]. Mahjoub *et al.* analyzed retrospectively patients with diabetes with normal renal function and found 41 % of patients with anemia [17]. Barbiere *et al.* reported an anemia prevalence of 34.2% among type 2 diabetic patients, although patients with deranged renal profiles were not excluded from that study [18]. Both studies reported a similar prevalence of anemia compared to our research. Contrary to our study, anemia was found in 7.21% of diabetics without diabetic nephropathy [19]. In the same way, another research that featured a diabetic patient with a normal renal profile found that the incidence of anemia was 15.3%, which is quite low [20]. A large number of individuals with inadequately managed diabetes may be the cause of the greater incidence of anemia in our investigation. Some research reported a relatively high prevalence of anemia, which is contrary to our findings. According to Pakistani research, 63% of individuals with type II diabetes mellitus were anemic [21]. In a different study, 65 of the 100 patients had anemia [22]. As both of these investigations included individuals with chronic kidney disease (CKD), the greater incidence may be explained by the fact that anemia is more noticeable in people with reduced renal functioning.

In our study 59.67±8.18 years was the participants' overall mean age. Krishnamurthy *et al.* found that the mean age was 53.4±13.6 years [4]. Another research found that the mean age of 55.5 ± 13.87 years [23]. A similar mean age of participants was reported, 49.64±13 years, in another study [12]. Interestingly, with a Mean of 62.29±6.33 years, 97% of anemic patients in our study aged more than 50 years which indicates a higher prevalence of anemia with advancing age.

In the study, there were 133 anemic patients: 45.9% were male and 54.1% were female, or a female-to-male ratio of 1.17:1. In another similar study there were 78 anemic patients: 30.7% were male and 69.3% were female, with female to male ratio of 2.3:1 [12]. Mahjoub *et al.* also stated that out of the 18 patients with anemia, 77.8% of the population is female and 22.2% is male [16]. Solomon *et al.* showed that the frequency of anemia in both genders was practically the same, *i.e.* 19.01% and 21.1% in males and females, respectively which is very much similar to our study [24]. Past research indicated an incidence of anemia in men up to 17-69% and in diabetic females, 11-30% [25, 26]. Our results, however, showed that females were more likely than males to get anemia.

Among 133 patients with anemia in our study, the majority had microcytic anemia, 41.1%, followed by macrocytic anemia 35.3% and normocytic anemia 23.3%. The higher frequency of microcytic hypochromic anemia in diabetes mellitus was probably caused by malnutrition, iron deficiency, and poverty. According to Joshi *et al.* normocytic anemia (28%), macrocytic anemia (16.8%), and microcytic anemia (55.5%) were the most prevalent types of anemia [27]. Comparably, another study demonstrated 16.6% macrocytic anemia and 42.3% each had microcytic and normocytic anemia [11]. According to another research, microcytic anemia was shown to be 31.2% more prevalent in diabetic individuals than normocytic anemia, which was found to be 64.4% more common [21]. According to Solomon *et al.* 81.4% of anemic individuals had normocytic hypochromic anemia [24]. Previous studies found a connection between normocytic normochromic anemia and long-term poorly managed diabetes in individuals without abnormal RFTs [28]. The variations seen in the aforementioned outcomes might be ascribed to distinct populations included in the studies.

With a mean diabetes duration of 10.45±3.79 years, 54.1%, had a duration of disease more than 10 years, 36.8% of anemic patients had a duration of 6-10 years whereas only 9% had a duration less than 5 years. This suggests that as the illness worsens, the chance of anemia increases ($P < 0.05$). A similar study showed among patients who were anemic the mean duration of diabetes was 9.05±4.99 [11]. Another study found that anemia affected 25 percent of patients with diabetes for a period of one year, 51.6% of those with diabetes for a period of one to five years, and 64 percent of those with diabetes for a period of six to ten years [22]. One theory puts forth that long-term hyperglycemia amplifies the control of transferrin receptors by glycation, which restricts the capacity of the receptors to bind iron and reduces the availability of iron [4]. Rathod *et al.* discovered that anemia was twice as common in individuals with diabetes for more than five years as it was in those with the disease for less than five years [29].

In our study, almost all the patients, 98.5%, with anemic had uncontrolled diabetes and only 1.5% of anemic

patients had controlled diabetes. In another study, there were 26 (33.3%) and 52 (66.7%) anemic individuals with managed diabetes and uncontrolled diabetes, respectively [11]. In one research, out of 11 diabetic patients with anemia, 10 patients had poorly controlled diabetes [30]. Similarly, Sharif *et al.* found that 13.5% of anemic patients had a HbA1C < 7.5% and 49.5% had a HbA1C > 7.5% [20].

Uncertainty surrounds the mechanisms behind anemia risk in poorly managed diabetes. Poor diabetes control is more common in patients with chronic diabetes, obesity, dyslipidemias, sedentary lifestyles, poor medication compliance, oral hyperglycemic drug and insulin use, improper diet chart following, and irregular glucose monitoring. Inadequate diabetes care leads to autonomic neuropathy in diabetes. Because erythropoietin production is partially regulated by the autonomic nervous system, individuals with inadequate glycemic control may have prematurely impaired production, according to the data. Anemia risk is further increased by systemic inflammation, chronic hyperglycemia, and low testosterone levels brought on by diabetes [30, 31].

CONCLUSION

In conclusion, there is a significant risk of anemia in people with type 2 diabetes mellitus who have normal renal function tests. Additionally, our research showed that among diabetes patients poor glycemic control, advanced age, and longer duration of illness dramatically raise the risk of anemia. Diabetic complications may be avoided if anemia in diabetic individuals is treated promptly. We think that part of the diabetes management guidelines ought to include frequent screening for anemia.

ETHICS APPROVAL

The study was approved by the ethical committee PNS Rahat Hospital (Reference # ERC/PNR/005/2023, 30/01/2023). All procedures performed in studies involving human participants were following the ethical standards of the institutional and/ or national research committee and the Helsinki Declaration.

CONSENT FOR PUBLICATION

Informed consents were obtained from all patients.

AVAILABILITY OF DATA

The data are not publicly available due to privacy or ethical restrictions but can be presented on request from the corresponding author.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Declared none.

AUTHORS' CONTRIBUTION

Khan MN: Conception and design of the study and revised it critically for important intellectual content. Data collection and supervised the statistical analysis did literature search, interpreted the results, drafted the manuscript and finalized it.

Nadeem H: Statistical analysis, literature search, interpretation of the results.

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