ORIGINAL ARTICLE

Newly Diagnosed Anemia in Admitted Diabetics, Frequency, Etiology and Associated Factors

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Abstract

Objective: To determine the frequency of newly-diagnosed anemia in diabetics admitted to the Internal Medicine Department and its etiology and contributing factors.

Study Design: A cross-sectional, analytical study.

Place and Duration of Study: Department of Internal Medicine, Sir Syed Trust Hospital and College of Medical Sciences, Karachi, from July 2011 to December 2012.

Methodology: Adult diabetic patients first diagnosed as having anemia upon hospital admission during the specified duration were included. Patients with active bleed, acute renal impairment, critical illness, pregnancy and previously diagnosed anemia were excluded. Etiology and risk factors of anemia were determined in each case on the basis of history, clinical findings and relevant laboratory investigations i.e. complete blood picture, red cell indices, iron profile, renal function tests, urine and stool examination. Association of anemia was determined using chi-square and t-tests with p-value < 0.05 taken as significant.

Results: One hundred and thirty patients (34 males and 96 females) were included. Mean age was 51 ± 12.4 years, with mean BMI of 25.4 ± 5.2 kg/m^2, mean duration of diabetes of 7.6 ± 5.5 years and mean glycated haemoglobin (HbA1c) 8.47 ± 1.58%, with 75% diabetics having unsatisfactory glycemic control. Mean haemoglobin was 11.6 ± 1.96 g/dl. Anemia was present in 63% diabetics (18 males and 64 females). It was normocytic in 59.8%, microcytic in 37.8% and macrocytic in 2.4%. Chronic Kidney Disease (CKD) was present in 44%, iron deficiency in 23%, mixed etiology in 6%, vitamin B-12 deficiency in 2% and thalassemia minor in 1% cases. Statistically significant association of anemia was found with poor glycemic control (p=0.002), dietary restriction for red meat (p < 0.001), history of blood loss (p < 0.001), gastrointestinal disorders (p < 0.001), CKD (p < 0.001) and retinopathy (p=0.011).

Conclusion: Anemia in two out of every three diabetics in this study points to need for haematological screening in all diabetics presenting to healthcare facility. In addition to chronic kidney disease, dietary iron and vitamin deficiency, glycemic control, presence of CKD, retinopathy and gastrointestinal disorders need to be evaluated and rectified.

Key Words: *Anemia. Chronic kidney disease. Diabetes mellitus. Dietary iron. Glycemic control. Retinopathy. Vitamin B-12.*

INTRODUCTION

Diabetes is still the leading cause of end stage renal disease, non-traumatic lower limb amputations and blindness among adults.[1] Currently, diabetes mellitus affects 240 million people worldwide and this number is expected to rise to 380 million by the year 2025, with 80% of the burden in low and middle income countries. Pakistan belongs to high prevalence area for diabetes, currently having 6.9 million affected people, with the estimates expected to double by 2025 and affect 11.5 million people.[2]

Anemia is an important component of diabetic nephropathy. It results from diminished erythropoietin production and to a lesser degree due to the increased excretion of erythropoietin in urine. However, erythropoietin responsiveness remains same in these patients.[3]

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Anemia in diabetes has complex and multifactorial etiology. Erythrocyte half-life is itself abnormal in diabetic patients due to several pathologies that have an impact on erythrocyte viability, such as increased osmotic stress on erythrocytes.[4] This leads to an overall short life span of erythrocytes in diabetics further contributing to anemia.

Patients with diabetes may be more vulnerable to the effects of anemia due to co-existent significant cardiovascular disease and hypoxia-induced organ damage. Haemoglobin levels may be linked to the risk of cardiovascular events, hospitalization, and increased mortality.[5] However, Cody *et al*.[6] suggested that there is no conclusive evidence that correction of anemia significantly improves the outcome in patients with failing renal function, apart from the quality of life.

Anemia has been associated with more adverse outcomes among diabetics. These include cardiovascular complications like left ventricular hypertrophy and congestive heart failure.[5] Studies have proved that correction of anemia improves cardiac function. The possible mechanism is by reduction of exercise-induced myocardial ischemia.[7]

In patients with diabetes, anemia has been associated with a progressive decline in renal function. Hypoxia caused by anemia stimulates renin-angiotensin-aldosterone system and contributes to renal vasoconstriction. These factors further exacerbate proteinuria by increasing protein in the renal tubules in diabetics. Treatment of anemia associated with diabetic kidney disease has also been shown to result in improvement in exercise capacity, physical performance features such as endurance, energy and physical mobility.

Because of lack of awareness, socioeconomic constraints and delayed referral to specialized centres, diabetic patients from our region frequently suffer complications. Also, due to multiple co-morbid conditions, poly-pharmacy and dietary constraints, generalized health of diabetics deteriorates further.[8]

The purpose of this study was to determine the frequency of newly diagnosed anemia and its various sub-types in admitted diabetics and its association with various risk factors.

METHODOLOGY

This cross-sectional analytical study was conducted at the Department of Internal Medicine, Sir Syed Trust Hospital and College of Medical Sciences, Karachi, from July 2011 to December 2012. After the ethical approval from institutional committee and patient's informed consent, adult diabetic patients (> 18 years age) admitted to Internal Medicine Department during the specified duration were included. Type 1 and type 2 diabetics of either gender were included. Seriously ill patients requiring critical care, patients having active bleed, pregnancy, evidence of acute renal impairment and previously diagnosed cases of anemia were excluded.

The demographic details were collected i.e. name, age, gender and address. Height and weight were measured and Body Mass Index (BMI) was calculated by the formula; weight (kg)/ height (m^2). Detailed clinical history was obtained. History of co-morbid conditions and reason for admission was documented. Duration of diabetes and history of diabetes related complications was taken. Patients were asked for dietary preferences, gastrointestinal disorders (i.e. acid peptic disease, gastro-esophageal reflux disease, altered bowel habits) and history of blood loss. A comprehensive clinical examination was performed including fundoscopy for diabetic retinopathy. Treatment history and list of medications used by patients were recorded. Patients were also asked about the use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), corticosteroids, anti-platelets, anticoagulants, proton pump inhibitors and antacids.

Patients were then investigated for presence of anemia. Complete blood counts were obtained including red cell indices. Anemia was diagnosed on the basis of WHO criteria.[9] Iron studies; including serum ferritin, iron and Total Iron Binding Capacity (TIBC) were advised. Those with iron deficiency were further investigated for the source of blood loss. Urea and creatinine levels were obtained and urine routine examination performed for albuminuria. Serum vitamin B-12 and folate levels were obtained in patients with macrocytic anemia. Estimated Glomerular Filtration Rate (GFR) was calculated using Cockcroft-Gault equation. In view of creatinine levels and albuminuria, patients were labeled as having CKD with estimated GFR as supporting evidence. All the investigations were comprehensively assessed in view of clinical history and laboratory evidence. Type of anemia and its etiology was diagnosed and documented for every patient. All the details were recorded on a specially designed proforma.

Data from questionnaire was analyzed using Statistical Package for Social Sciences (SPSS) version 17. Mean and standard deviation was calculated for quantitative variables like age, BMI, HbA1c and duration of diabetes. Frequencies and percentages were calculated for qualitative variables like history of blood loss, gastro-intestinal complaints, retinopathy, ischemic heart disease, and use of various medications. The outcome of anemia was labeled as present or absent with cut off value of 12 g/dl for females and 13 g/dl for males as per WHO criteria.[9] Glycemic control labeled as unsatisfactory at HbA1c > 7%.[10] Pearson's chi-square test was used to compare categorical variables. The t-test was applied for comparison of mean values of age and BMI. P-value < 0.05 was considered as statistically significant.

RESULTS

A total of 130 patients with diabetes were included (34 males and 96 females). Mean age was 51 ± 12.4 (18 - 85) years with mean BMI of 25.4 ± 5.2 (13 - 38) kg/m^2 and mean duration of diabetes being 7.6 ± 5.5 years. Mean HbA1c was 8.47 ± 1.58%, with unsatisfactory glycemic control in 75% of diabetics.

Most common reasons for admission were various infections (38%) and inadequate diabetic control (23%). Co-morbid conditions in these patients were hypertension (n=59), ischemic heart disease (n=41), Hepatitis-C (n=12), Hepatitis-B (n=2), cerebrovascular accident (n=6), tuberculosis (n=6) and hypothyroidism (n=2).

Mean haemoglobin was 11.6 ± 1.96 g/dl (12.5 g/dl in males and 11.2 g/dl in females). Out of 130 patients, 82 (63%) were diagnosed to have anemia, that included 18 males (53% of male diabetics) and 64 females (66% of female diabetics) having no statistically significant association of anemia with gender (p=0.154). Among these, normocytic anemia was present in 59.8% of anemia; 73% of them had evidence of CKD. Microcytic

anemia was found in 37.8%; 61% of them had iron deficiency, 13% had CKD, 16% had co-existing CKD and iron deficiency, 1% had thalassemia minor. Macrocytic anemia with vitamin B-12 deficiency was found in 2.4%. The remaining 19 patients (23% of anemics) were classified as other causes. Among them, 5 patients had evidence of other chronic systemic disease. However, the cause of anemia remained unexplained despite of workup in 14 patients (Figure 1 and 2).

Unsatisfactory glycemic control was present in 69 (84%) of diabetics with anemia as compared to 29 (60%) of diabetics without anemia. Significant association was found between poor glycemic control and anemia in diabetics (p=0.002).

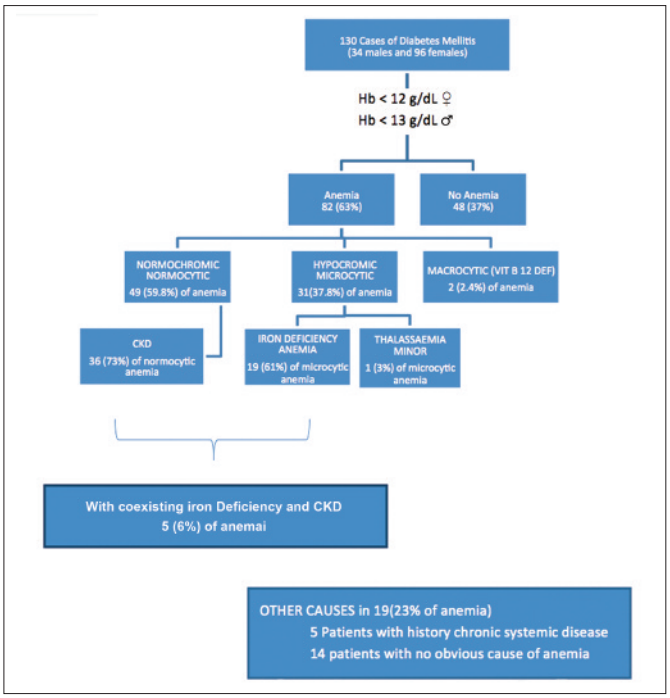

Figure 1: The etiological sub-types of anemia seen among diabetics in study group (n=130).

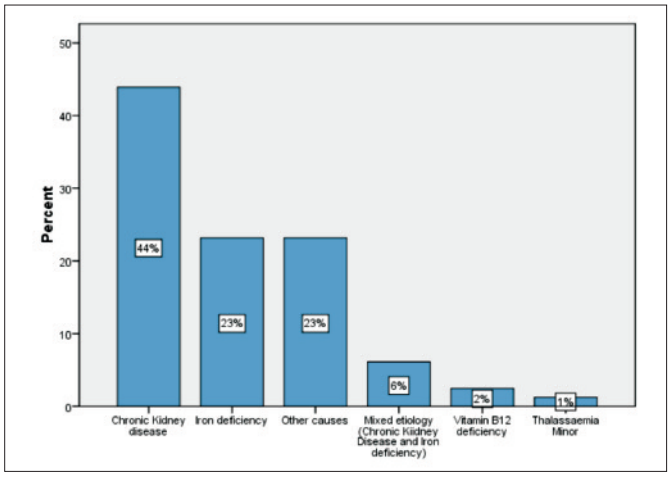

Figure 2: Bar graph presentation of etiology of anemia in diabetes (n=82).

There was a history of gastrointestinal disorder (acid peptic disease, GERD, altered bowel habits) in 46% diabetics having significant association with anemia (p=0.001). History and evidence of blood loss was present in 18.4% patients (gastrointestinal blood loss in 5%, menorrhagia and gynecological blood loss among 11% of females). However, 81% patients had no evidence of blood loss. Significant association between history of blood loss and anemia was present (p < 0.001).

According to dietary preferences, 5.4% of the patients were strict vegetarians, 52% taking white meat and vegetables (with restriction of red meat) and 42% with mixed dietary intake (including red meat). Anemia was significantly higher in patients taking white meat and vegetables (82%) as compared to those taking mixed diet (38%, p < 0.001).

Use of antacids and proton pump inhibitors was found in 67% patients, NSAIDs in 35%, anti-platelets in 35%, Angiotensin Converting Enzyme (ACE) inhibitors/ Angiotensin Receptor Blockers (ARBs) in 31%, corticosteroids in 7.7%, anticoagulants in 1% with no significant association of any of these with anemia (p > 0.05).

Table I: Frequency of various variables and their association with anemia.

Variables	Anemia (n=82)	No Anemia (n=48)	p-value
Age (mean ± SD)	52.6 ± 12.3	49 ± 12.5	0.899**
Gender			
Male	18 (22%)	16 (33%)	0.154*
Female	64 (78%)	32 (67%)	
BMI (mean ± SD)	25.9 ± 5.4	24.6 ± 4.9	0.633**
Glycemic control			
Satisfactory (HbA1c < 7%)	13 (16%)	19 (40%)	0.002*
Unsatisfactory (HbA1c > 7%)	69 (84%)	29 (60%)	
Gastrointestinal disorder	47 (57%)	13 (27%)	0.001*
History of blood loss	22 (26%)	2 (4%)	<0.001*
Dietary intake			
Vegetarians	5 (6%)	2 (4%)	<0.001*
White meat and vegetables	56 (68%)	12 (25%)	
Mixed diet	21 (26%)	34 (70%)	
NSAIDs	32 (39%)	14 (29%)	0.257*
Antiplatelet drugs	28 (34%)	18 (37%)	0.700*
Anticoagulants	1 (1%)	0 (0%)	0.442*
Corticosteroids	6 (7%)	4 (8%)	0.834*
Antacids/PPI's	56 (68%)	31 (65%)	0.664*
ACE inhibitors	27 (33%)	14 (29%)	0.656*
Mode of treatment			
Oral hypoglycaemics	33 (40%)	26 (54%)	0.382*
Dietary control only	5 (6%)	1 (2%)	
Insulin therapy	21 (25%)	11 (23%)	
Combined insulin and oral therapy	23 (28%)	10 (21%)	
Ischemic heart disease	26 (32%)	15 (31%)	0.957*
Retinopathy	41 (50%)	13 (27%)	0.011*
Chronic kidney disease	41 (50%)	0 (0%)	<0.001*
Albuminuria	49 (60%)	21 (43%)	0.077*

**Test of significance chi-square's test; **Test of significance independent sample t-test; p < 0.05 considered significant.*

Regarding the mode of treatment for diabetes, dietary control alone in 4% patients, oral hypoglycaemics in 45%, insulin therapy in 24% and combination therapy in 25%. There was no significant association of mode of treatment with anemia (p=0.382).

Ischemic heart disease was found in 32% patients having no significant association with anemia (p=0.957). Retinopathy in 50% having significant association with anemia (p=0.011). Half (50%) of the patients had evidence of CKD having significant association with anemia (p < 0.001, Table I).

DISCUSSION

Anemia is frequently seen in diabetics and very often remains undiagnosed. WHO reports global prevalence of anemia in general population to be 24.8% (12.7% in males and 30.2% in females). The highest prevalence area being reported is Africa (47.5%) and South-East Asia (35.7%).[11] Bonakdaran *et al*.[12] found anemia in 19.6% of diabetics and Goldhaber *et al*.[13] in 32%. Thus suggesting approximately 3 - 4 times higher prevalence of anemia in diabetics from Pakistan.

Ranil *et al*.[14] found anemia in comparatively higher number of females with diabetes (26%) versus males (10%). This gender difference was less marked in this study possibly because of prevalent nutritional deficiencies and diabetes related complications even in males from lower socioeconomic class. This suggests that diabetic males should also be considered to be at risk for anemia.

Mean duration of diabetes of 7 years in this study indicates long standing diabetes in most of the studied patients, thus imposing them to higher risk of diabetic complications. Mean BMI observed (25.4 kg/m^2) is in accordance with the recommendations of American Diabetic Association (ADA). High BMI is associated with increased prevalence of diabetes mellitus, hypertension and dyslipidaemia.

It is suggested by ADA that HbA1c < 7% reduces the micro-vascular and neuropathic complications in diabetes.[10] In this study, 75% of diabetics had poor glycemic control that is significantly associated with anemia. There is a need to educate patients and adjust their treatment regimens. Adoye *et al*.[15] concluded that in the presence of anemia (particularly iron deficiency), there may be over estimation of HbA1c levels. As there was significant number of patients with iron deficiency anemia in this study, the authors suggest that results should be interpreted carefully.

Jessani *et al*.[16] reported prevalence of CKD as 12.5% in Pakistani adults. Anemia in association with CKD contributed to 50% of anaemia, hence major cause of anemia in this study. This figure is almost double as compared to the prevalence of 25% documented by Janmohamed *et al*.[17] This could possibly be due to higher prevalence of diabetic kidney disease in these patients.

Iron deficiency was found in among 23% of diabetics with anemia, which is higher than the figure of 15.5% reported by Sharif *et al*.[18] However, Katherine *et al*.[19] found iron deficiency in none of their diabetic patients in a study conducted in UK. Higher prevalence of iron deficiency in these diabetics may be the reflection of higher prevalence of iron deficiency in Asian countries.[20] Other possible reasons could be that most of the patients that presented belong to lower socioeconomic class who frequently has nutritional deficiencies, lack of awareness and inability to access appropriate health-care due to financial constraints.

Anemia in patients taking white meat and vegetables in this study was almost double as compared to those taking mixed diet. Thus dietary restrictions of red meat should be substituted by alternate sources of iron in diabetics like spinach, apples, sea food, beans and whole grain.

Despite of workup, a quarter of patients remained undiagnosed in this study. Trevest *et al*. suggested that anemia is prevalent in elderly diabetics.[21] Older age and prolonged duration of diabetes are predictors of anemia in this age group and CKD is a mediator. Several mechanisms including erythropoietin insufficiency are still being investigated. Most of the studied patients belonged to older age group with prolonged duration of diabetes that could be the possible additional contributing factor for unexplained anemia.

Micro-vascular complications are frequently seen in uncontrolled and long standing diabetes. Significant association was found between anemia and retinopathy as well as nephropathy. Ranil *et al*. found anemia to be a risk factor for presence and severity of diabetic retinopathy.[14] Vlagopoulos *et al*. concluded that low haemoglobin levels in diabetics increase the risk for progression of kidney disease and cardiovascular morbidity and mortality.[22] Significant association of anemia with retinopathy and nephropathy in this study suggest that timely diagnoses and management of anemia may reduce the micro-vascular complications in diabetes.

Gastrointestinal disorders (acid peptic disease, GERD, altered bowel habits) were present in almost half of diabetics having significant association with anemia. Poor appetite secondary to gastrointestinal disorders or poly-pharmacy; altered gut absorption and motility disorders could be the possible reasons.

Diabetics often suffer from multiple co-morbid conditions. Possibly because several diseases like hypertension and ischemic heart disease share the same risk factors as diabetes. Poly-pharmacy is frequent among diabetics that may contribute to anemia directly or indirectly. Marathias *et al*. found ACE inhibitors and ARBs to be associated with reversible decrease in haemoglobin concentration in diabetics.[23] Contrary to that Dousdampanis *et al*. negated this and his study also suggests the same.[24]

Several trials conducted on benefits of treating anemia in diabetics suggest that correction of anemia leads to improved quality of life in diabetics.[25] Silverberg *et al*. found that in patients with congestive cardiac failure, correction of anemia leads to improved heart function, stabilized renal status and markedly reduced need for hospital admissions.[7]

Most of the diabetics are unaware of the presence of anemia. This study was conducted on indoor patients and authors suggest the need for assessment in outdoor patients. Limitations of this study are that most of the patients are from lower socioeconomic class, lack of randomization and inability to perform expensive laboratory investigations (e.g. erythropoietin levels). Etiology of anemia in diabetes being multifactorial with several risk factors to be assessed and evaluated, hence results of this study should be interpreted carefully and authors recommend further regional studies to verify these results particularly in terms of gender, glycemic control and mixed etiology of anemia.

CONCLUSION

Anemia in two out of every three diabetics in this study points to the need for haematological screening in all diabetics presenting to healthcare facility. In addition to chronic kidney disease, dietary iron and vitamin deficiency, glycemic control, presence of CKD, retinopathy and gastrointestinal disorders need to be evaluated and rectified.

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