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**(Original Article)**

# Study of Anemia in Diabetics

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**ABSTRACT**

*Diabetes is the leading cause of chronic kidney disease (CKD) and is associated with excessive cardiovascular morbidity and mortality.[1,2] Anaemia is common among those with diabetes and CKD and greatly contributes to patient outcomes.[3,4] Observational studies indicate that low Hb levels in such patients may increase risk for progression of kidney disease and cardiovascular morbidity and mortality.[5] Controlled clinical trials of anemia treatment with erythropoietin stimulating agents (ESAs) demonstrated improved quality of life (QOL) but have not demonstrated improved outcomes. [6,7] In some trials, ESA treatment for high Hb levels is associated with worse outcomes such as increased thrombosis risk.[6,8] Consequently, the U.S. Food and Drug Administration (FDA) and the National Kidney Foundation (NKF) have modified their recommendations regarding anemia treatment for CKD patients.[9]*

*The objectives of this review are.*

*1) To evaluate the presence of anaemia in patients with diabetes mellitus. And*

*2) To study the effect of anaemia and its complications in diabetes mellitus.*

**Methods:** *The present study is a prospective observational study designed to evaluate the presence of anaemia, effect and complications in diabetes mellitus.*

## INTRODUCTION

Diabetes is the most common cause of chronic kidney disease (CKD) in the world, present in nearly two thirds of all patients with renal impairment.[10] Anaemia is a most common complication of CKD, affecting over half of the patients.[10,11] Consequently, diabetes is also the most common cause of renal anaemia. However, over-and-above diabetes is simply a cause of renal disease; anaemia is also more common in patients with diabetes than those with renal disease of other causes. Anemia occurs early in the development of kidney disease and worsens with declining kidney function. Many studies have demonstrated an association between the Hb concentration and kidney function. One of the largest, the Third National Health and Nutrition Examination Survey (NHANES III), examined more than 15,000 people in the general U.S. population between 1988 and 1994 and found an inverse relationship between GFR < 60 ml/min/ 1.73 $m^2$ and prevalence of anemia. Using estimated GFR, the prevalence of anemia, defined as an Hb concentration < 12 g/dl in men and < 11 g/dl in women, increased from 1% in patients with a GFR of 60 ml/min per 1.73 $m^2$ to 9% at a GFR rate of 30 ml/min/1.73 $m^2$ and to 33% for men and 67% for women at a GFR of 15 ml/min/1.73 $m^2$.[12,13]

Although it is known that anaemia is common in patients with CKD, the impact of diabetes on the prevalence of anemia in patients with CKD has not been well established. In a recent study, three groups of patients were compared: those with type 2 diabetes without CKD ($n$ = 75), those with type 2 diabetes and CKD ($n$ = 106), and those with CKD without diabetes ($n$ = 100). The investigators found that, although anaemia was most common in patients with CKD and diabetes (70.5%), it was also present in 16% of patients with diabetes alone. In patients with CKD Stages 4 and 5, the prevalence of anaemia was significantly higher in those with diabetes compared with those who did not have diabetes. The authors noted that a higher awareness of the prevalence of anaemia in patients with CKD and diabetes will allow earlier diagnosis and treatment.[14]

**REVIEW OF LITERATURE**

Al-Salman M et al[15] studied 227 diabetic patients with demographic profile, history of stroke, ischemic heart disease (IHD) and concomitant hypertension (HT) along with the most recent values of complete blood picture and renal function tests. The study had prevalence of anaemia in 55.5% population with half of the population with stage-I kidney disease. It concluded that anaemia is a common accompaniment with diabetes and it is seen early even in the absence of renal impairment which necessitate early screening of anaemia and further studiesto know the possible etiology.

Adiv Goldhaber et al[16]conducted a cohort study done in primary care clinic setting among 594 patients. Out of these, 192 (32%) had anaemia with normal creatinine levels. They concluded that the factors associated with anaemia were older age, higher serum creatinine level and use of glitazone therapy.

Kuriyama et al.[17]studied 106 patients with stage 3–4 CKD with or without anemia. Those with anemia were randomized to ESA treatment or no treatment. The time to a doubling of serum creatinine from baseline was the study's primary end point. They found that time to doubling of serum creatinine was significantly longer in the treated group than in the nontreated group and similar to that in the nonanemic control subjects[17].

Gouva et al[18]randomized 88 anemic stage 3–5 CKD patients to early versus late treatment with erythropoietin-α to test the hypothesis that this intervention would slow the rate of progression to end-stage renal disease (ESRD). They found that early correction of anemia was associated with improved renal and patient survival compared with delayed treatment of anemia.

Rossert et al.[19] performed a randomized controlled trial involving 390 patients with stage 3–4 CKD and anemia to test the hypothesis that treatment of anemia with an ESA to reach a higher Hb level would slow decline in kidney function. Subjects were targeted to one of two Hb levels (13–15 or 11–12 g/dl) and followed for 12 months. Although the decline in GFR was numerically less in the high-Hb group, this difference was not statistically significant. Still, those randomized to the high group showed improvement in QOL and vitality[19].

However, the two largest trials to date to examine the effect of ESA on progression of kidney disease (as a secondary outcome) did not show any renal benefit of raising Hb to a higher level.

Ritz et al.[20] randomized 172 anemic patients with type 1 or type 2 diabetes and stage 1–3 CKD to treatment with epoetin-α and a target Hb level of either 13–15 or 10.5–11.5 g/dl and followed them for 19 months. The primary outcome was the change in left-ventricular mass index, and secondary outcomes included kidney function and QOL. There were no significant differences in left-ventricular mass index in those randomized to the higher target; however, QOL measures were significantly better in the higher Hb arm. There were no differences in kidney function decline and no significant differences in adverse events.

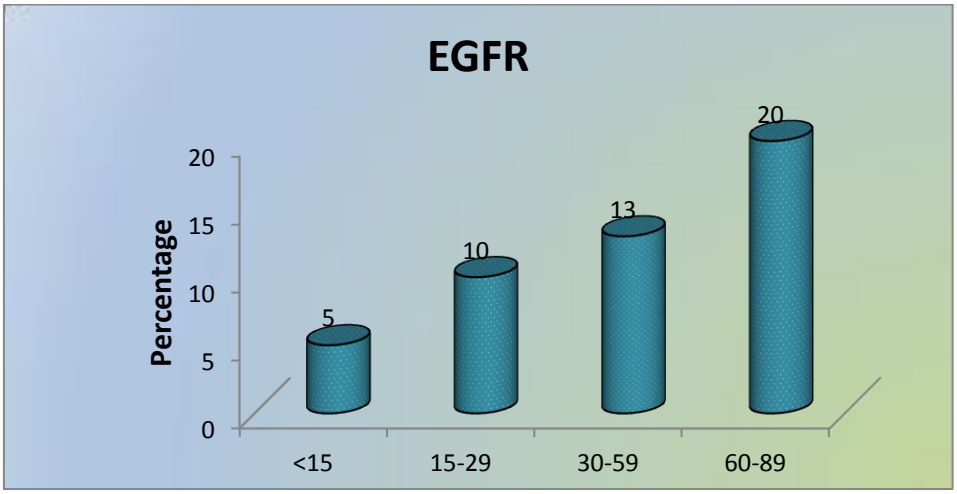
**RESULTS**

In a prospective observational study of 100 patients with diabetes mellitus, with the aim to study

Presence of anaemia, following results were obtained.

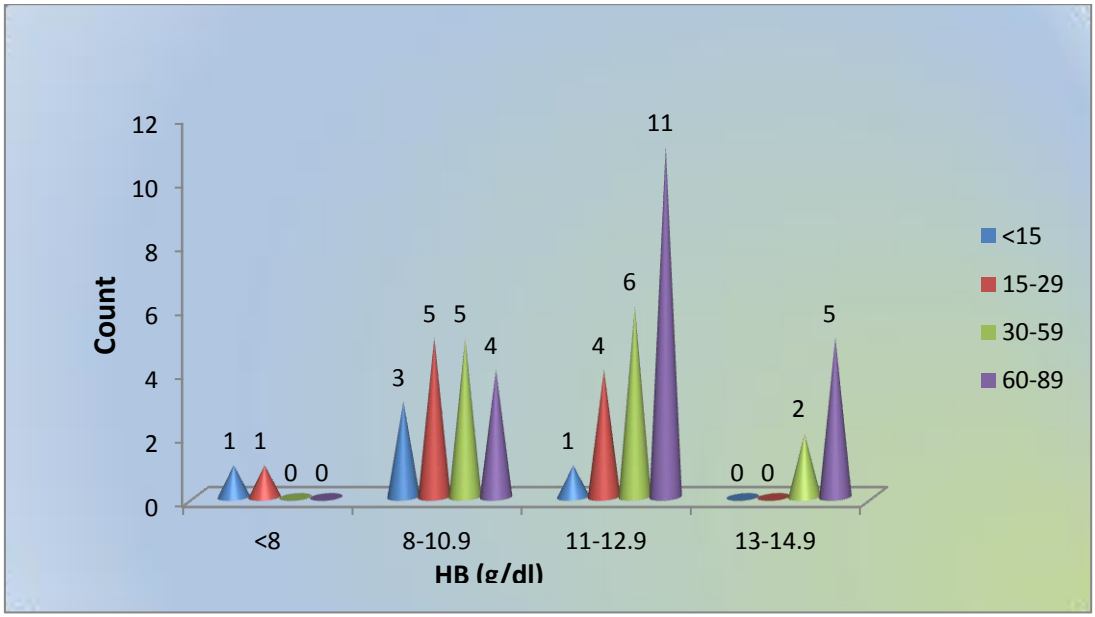
1. The maximum number of patients 35 (35%) belonged to age group 51-61 years, while 25 (25%) belonged to above 61 years group and there were 9 patients in 29-39 years of age. Mean age was 50-47 years and standard deviation of 13.98
2. Male patients were 46% and females were 54%.
3. Out of the total (100 patients) number of patients, maximum number of patients 46(46%) were seen to have diabetes for the duration of 4-8 years, whereas only 3 patients had diabetes for more than 12 years.
4. The maximum number of patients had type 2 Diabetes mellitus 95(95%) and only 5 patients were type I diabetes mellitus (5%).
5. The maximum number of patients were seen to have fasting blood glucose ranging from 176-225mg/dl, that is 51(51%). Most of the patients had an average glycemic control.
6. The maximum number of patients were seen to have hemoglobin levels between 11-12.9, 42 (42%), that is mild anaemia, whereas 29(26%) had moderate anaemia with Hb ranging from 8-10.9 and only 2(2%) patients had severe anaemia with Hb<8gm/dl.
7. The maximum number of patients were seen to have mild anaemia with Hb ranging from 11-12.9, 16 (47.1%) amongst the total anemic males.
8. The number of females with significant anaemia ranging from Hb 8-10.9 is more 17(39.5%) as compared to females with mild to moderate anaemia.
9. According to this study, 56(56%) diabetics were anemic, out of the total 100 subjects.
10. Out of the total number of anemic, 39(69%) patients had normocytic normochromic anaemia, 2(3.6%) had macrocytic anaemia and 15(26.8%) had microcytic anaemia.
11. Total patients were seen to have EGFR<90 and were seen to have CKD between stage 1 to 4 whereas 52(52%) of the remaining patients had normal EGFR.
12. In this study, hypertension was seen with anaemia with a total of 31 subjects who are anemic and hypertensive.
13. Out of the total of 100 patients, 55 were using metformin, of which 14 were anemic females and 13 were anemic males. We saw two patients out of 56 were having macrocytic anemia with metformin use.

**GRAPH NO.1**-Estimated Glomerular Filtration Rate



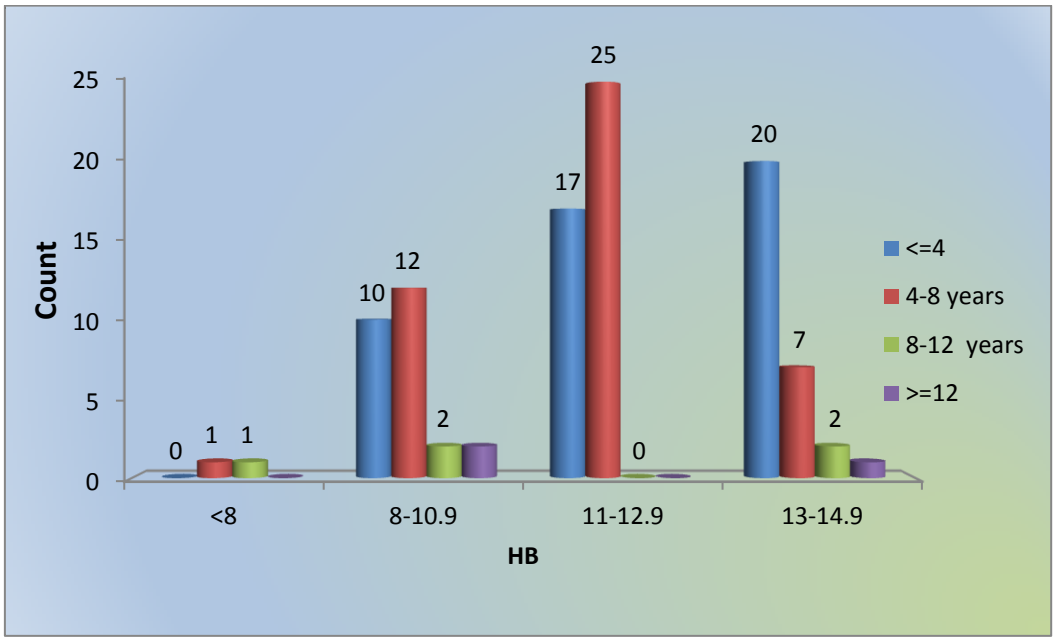

This figure shows total 48(48%) patients were seen to have EGFR<90 and were seen to have CKD between stage 1 to 4 whereas 52(52%) of the remaining patients had normal EGFR.

**GRAPH NO.2-**Anaemia with CKD




This figure shows the maximum numbers of patients were seen to have EGFR between 60-89(11) that is stage 1 CKD with Hb ranging between 11-12.9 that is mild anaemia. Patients with stage 2-4 CKD have Hb ranging from 8-10.9 or less than 8gm/dl.

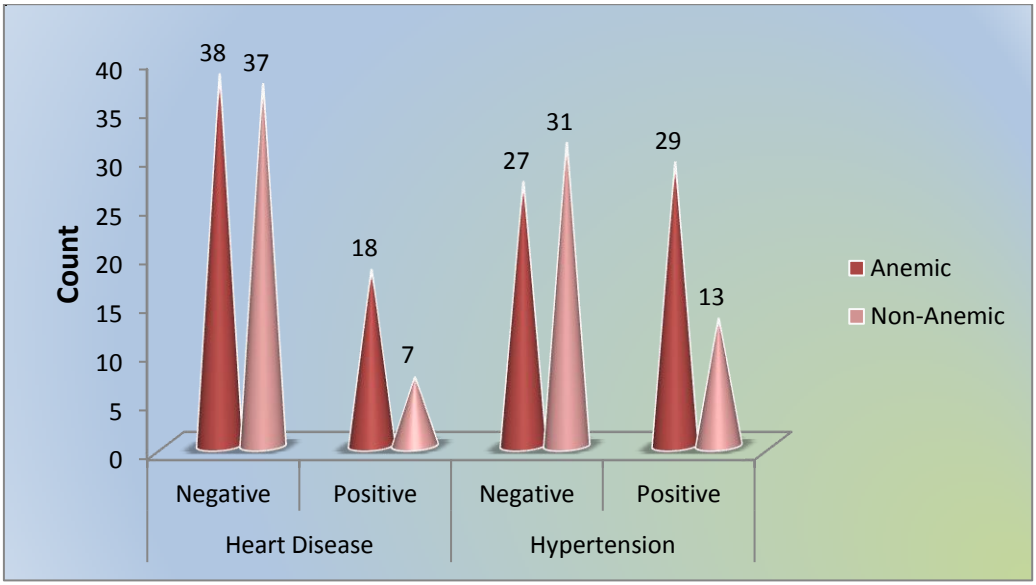
**GRAPH NO.3-** Anaemia with duration of DM




This figure shows p=0.006, using Chi square, p value =0.006 <0.05. Hence Hb and duration of DM are dependent.

According to the study, as the duration of diabetes progresses, the prevalence of anaemia increases. Maximum number of anemic diabetics were found between the duration of 4-8 years of diabetes.

**GRAPH NO.4**-Comparison of Presence of Microvascular Complications with Anemia




This figure shows the microvascular complications like hypertension were seen to be more prevalent in patients with anaemia.

**DISCUSSION**

Even though diabetes mellitus is one of the rising disorders in our country, awareness and research about diabetes mellitus causing anaemia and other microvascular complications is lacking.

The present study conducted at a tertiary care centre in Navi Mumbai, included 100 cases of diabetes mellitus. Similarly, Al Salman et al[15] conducted a study in Department of Internal Medicine, King Faisal University, Hofuf, Saudi Arabia on "Anaemia in presence of Diabetes Mellitus Prevalence and Progression" on 227 patients.

The results in the present study were consistent with other studies, where diabetes was prevalent more among older population. The number of females outnumbered the males. The reason for this distribution predominantly among older females is that females are more often obese and less physically active.

The presence of anaemia in diabetes in the study conducted by Al-Salman M et al[15] shows 55.5% patients to be anemic which is comparable to our study with 56%. According to our study, most of the anemic had MCV between 80-100 that is 69.9%, which is normocytic. This is comparable to the study done by Al-Salman M et al which shows 53.2% of population normocytic.

The patients with normal EGFR in our study i.e. more than 90, outnumbers the patients with CKD between stage 1-4 with 52%, which is unlike the study of Al-Salman M et al[15] which has more number of patients with CKD with EGFR less than 90 with 59.9% population. In our study, the patients with EGFR <90 were 48% of which 34 patients (70.1%) patients were anemic and 14 patients (21.6%) were non-anemic. This is comparable to the study of Al-Salman M et al which shows 88(64.7%) had anaemia while 48 (35.3%) had nio anaemia amongst the patients with impaired kidney function.

The distribution of EGFR and the presence of kidney disease is to evaluate that anaemia is seen is diabetes patients even if the kidneys may or may not have the dysfunction. Thus early diagnosis of anemia with diabetes is independent of the involvement of kidney, although the presence of kidney dysfunction is mostly associated with anemia.

The presence of microvascular complications like hypertension was seen more in the presence of anaemia i.e.40% which is incomparable to the study done by Al-Salman M et al that is 60.8%.Presence of heart disease amongst patients with anaemia is seen to be 25% in per study,

which is in comparison to the study of Al-Salman M et al which has 22% patients with heart disease. Most of the parameters in our study were in correlation with the previous study of Al-Salman M et al[15] Our study is consistent with the presence of anemia, the type of anemia and the involvement of kidney dysfunction and other microvascular complications.

However, these studies also included other parameters (EPO levels, iron studies, complications like stroke) amongst patients which was not seen in our study.

## CONCLUSION AND SUMMARY

The present study was conducted with the aim to study anaemia in diabetes mellitus which was seen more in older patients. The female patients were affected more with anemia as compared to male. 95% of the patients studied were of type 2 diabetes mellitus. 51% patients had moderate glycemic control whereas others had moderate to poor glycemic control.

Diagnosis of anaemia was done within early years of the disease, which is 4-8 years. Therefore, we concluded that assessment and further evaluation of anaemia should be done in all the diabetics even in the initial period of the disease.

The predominant type of anaemia seen in our study was normocytic, which shows that diabetes mellitus does not bring about any change in the morphology of the red cells. Anaemia was prevalent in patients with kidney dysfunction, but in our study it was seen before the kidney functions were affected in diabetes.

Microvascular complications like hypertensiuon, heart disease and CKD were highly associated with anaemia with diabetes. So, anaemia may have further role in the development and progression of both micro and macrovascular complications.

Drug therapy in diabetes, especially the use of metformin was seen to have association with macrocytic anaemia on 2 patients in our study, which may be due to vitamin B12 deficiency caused by metformin. Further evaluation to conclude this was not done in our study.

Anemia is common and contributes to both poor QOL and increased risk for adverse outcomes including death. Treatment of anemia improves QOL; however, thus far, evidence is lacking for a benefit of anemia treatment on progression of kidney disease and cardiovascular outcomes. Untreated anaemia of CKD is strongly associated with cardiovascular and renal complications, resulting in increased hospitalisations and mortality. Therefore, correcting anaemia is considered an important part of slowing or even stopping the progression of CKD.[21] Treatment with recombinant human erythropoietin in pre-dialysis patients corrects anaemia, avoids the requirement for blood transfusions and also improves quality of life and exercise capacity.[22,23]

## RECOMMENDATIONS

Additional randomized clinical trials are needed to more precisely define these parameters for an individual patient. Future studies are also needed to elaborate the mechanisms of anemia in patients with diabetes and CKD including the role of iron metabolism, inflammation, and resistance.

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**"The secret of health for both mind and body is not to mourn for the past, worry about the future, or anticipate troubles, but to live in the present moment wisely and earnestly".**

**- Buddha**