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Anemia profile in Diabetic patients with preserved renal function

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ABSTRACT

Background: Diabetes is one of the largest global health emergencies of the 21st century. Prevalence of anemia in diabetic patients is two to three times higher than for patients with comparable renal impairment and iron stores in the general population. **Aims and Objective:** This study was done to analyse the prevalence of anemia and its profile in patients with preserved renal function. **Materials and Methods:** One-hundred diabetic patients with anemia with normal renal functions were selected. Complete blood count, peripheral blood smear, iron studies, vitamin B12 levels were assessed. Diabetic control was monitored by HbA1c. Patients were identified to have specific type of anemia, based on iron profile and vitamin B12 levels. Severity of anemia was also assessed. Appropriate statistical tests were applied to analyse the results. **Results:** Mean age of subjects in the study group was 53.4 ± 13.6 years. The mean haemoglobin level was 9.41 ± 2.18 g/dl. Out of the 100 cases, 43 patients had iron deficiency anemia, 40 patients had anemia of inflammation, and 8 patients had vitamin B12 deficiency, 8 patients had combined iron and vitamin B12 deficiency, and 1 patient had pancytopenia. Mean HbA1c was higher in iron deficient individuals with a significant p value and mean HbA1c was lower in Vitamin B12 deficient individuals. Among the cases, 16% had mild anemia, 61% had moderate anemia, and 23% had severe anemia. Severe anemia had a significantly lower HbA1c, which was statistically significant. **Conclusion:** According to our study, iron deficiency anemia was the commonest, followed by anemia of inflammation in diabetic patients with preserved renal function. Diabetes being a pro-inflammatory state had a higher incidence of anemia of inflammation compared to general population. We have to identify and acknowledge the higher prevalence of Anemia of Inflammation in diabetic patients in the absence of renal dysfunction.

Key words: Anemia; Diabetes; Preserved renal function; Anemia of Inflammation

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INTRODUCTION

Diabetes is one of the largest global health emergencies of the 21st century. About 415 million adults are estimated to currently have diabetes worldwide.[1] Anaemia is a common occurrence in diabetes, particularly in those with albuminuria or impaired renal function. It has various implications including potentially contributing to the pathogenesis of diabetic complications. In India, according to a study done at Gandhinagar, 18% of diabetics were anemic with 74% of anemic patients having a serum creatinine <110μmol/l and 72% of anemic patients with a calculated creatinine clearance of >60 ml/min.[2] Prevalence of anemia is two to three times higher in diabetics than for patients with comparable renal impairment and iron stores in general population.[3] Notably, the prevalence of anemia was increased by diabetes, even in patients with preserved renal function.[3]

The etiology and pathogenesis of anemia in diabetes is multifactorial. These factors include diabetic nephropathy, chronic inflammation, elevated levels of advanced glycation end products, iron deficiency, antidiabetic medications, diabetic neuropathy, and low testosterone levels.[4] Chronic hyperglycaemia might result in impaired deformability of red blood cells, oxidative stress, and sympathetic denervation of the kidney related to autonomic neuropathy. These factors promote a hypoxic environment in the renal interstitium, which leads to impaired production of erythropoietin by the

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peritubular fibroblasts. Inappropriately low erythropoietin level is an important cause of early anemia in patients with diabetes mellitus.[5]

Anemia is an independent risk factor for the development and progression of cardiovascular disease,[6] congestive heart failure,[7] and chronic kidney disease,[8] and a potential contributing factor to the development and progression of diabetic retinopathy[9] and other diabetic complications. Hence this study was done to identify the haematological profile of anemia in diabetic patients with preserved renal function.

MATERIALS AND METHODS

This was a cross sectional observational study done at a Tertiary care Medical college hospital. One-hundred diabetic patients were recruited into the study after taking an informed consent. Ethical approval was obtained from the Institutional ethics committee.

Inclusion criteria was diabetic patients with anemia defined as Hb < 13g/dl in men and Hb < 12g/dl in women with duration of diabetes being more than 1 year.

Exclusion criteria were renal dysfunction assessed by proteinuria and calculated eGFR <60 mL/min/1.73 m2; acute blood loss; pregnant women and gestational diabetes mellitus; acute kidney injury; acute infections.

Complete blood count, peripheral blood smear, iron studies, vitamin B12 levels were assessed. Diabetic control was also monitored by blood sugar levels and HbA1c. Patients were identified to have specific type of anemia, based on iron profile and vitamin B12 levels.

In our study Iron deficiency anemia (IDA) was diagnosed when S.iron <45 mcg/dl, TSAT <20%, ferritin <30mcg/L, TIBC >450mcg/dl. Anemia of Inflamation (AI) was diagnosed with S.Iron-low, TSAT-low or normal, ferritin >100mcg/L, TIBC-low. B12 deficiency was diagnosed when less than 185pg/ml.

The qualitative variables were presented as frequencies and percentages and quantitative variables as average and standard deviation or median. Student's -test was used for normally distributed variables, and the Chi-square test was used to compare categorical variables.

RESULTS

Mean age of subjects in the study group was 53.4±13.6 years. Out of 100 patients, 49 patients were male and 51 patients were female.

The mean haemoglobin level, PCV, MCV, MCH, MCHC, HbA1c was 9.41±2.18 g/dL, 28.7±6.73, 79.89±10.2 fL, 25.7±4.48 pg/dL, 32.4±5.44 g/dL, 9.91±3.13 respectively.

Out of the 100 cases, 43 patients had iron deficiency anemia, 40 patients had anemia of inflammation, and 8 patients had vitamin B12 deficiency, 8 patients had combined iron and vitamin B12 deficiency, and 1 patient had pancytopenia which required further evaluation. This is depicted in Figure 1.

Mean hemoglobin in IDA was 8.75g/dl, in AI was 10.57g/dl, and in vitamin B12 deficiency was 8 g/dl. Mean HbA1c of IDA was 10.58g/dl, of AI was 9.23g/dl, of vitamin B12 deficiency was 9.11g/dl.

Among the cases, 79% had serum iron of <45µg/dl, and 21% have serum iron of >45µg/dl. Mean HbA1c in iron deficient individuals is 10.23, whereas in iron sufficient individuals is 8.67, with a significant p value of 0.042. Scatterplot of the same has been depicted in Figure 2.

Among the cases, 83% had a vitamin B12 level of >185 pg/ml, whereas 17% had a level of <185 pg/ml. Mean HbA1c in vitamin B12 deficiency is 9.61 whereas in vitamin B12 sufficient individuals is 9.96, though p value was not significant. Scatterplot of the same has been depicted in Figure 3.

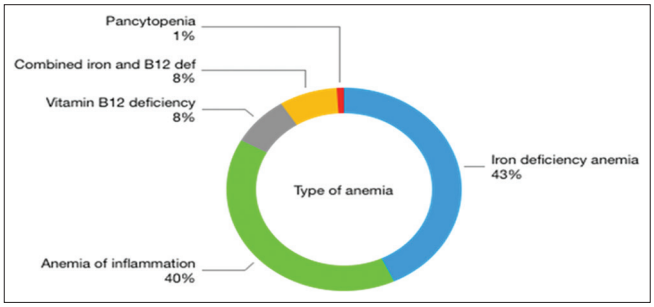

Figure 1: Percentage of patients with different types of anemia

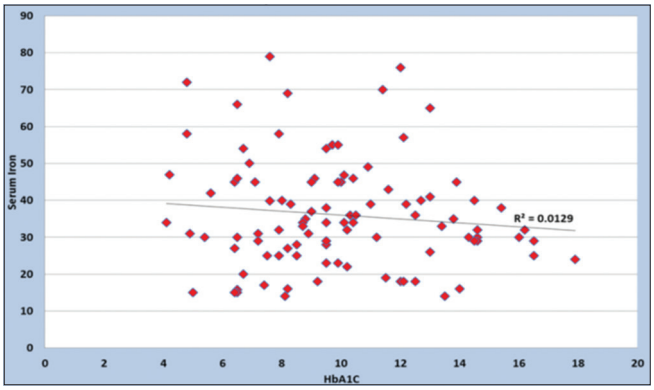

Figure 2: Scatterplot of HbA1c vs S. Iron

Anemia was characterised as mild, moderate and severe according to WHO criteria i.e. severe anemia where Hb was <8 g/dl, moderate anemia where Hb was 8-10.9 g/dl and mild anemia wherein Hb was 11-11.9 g/dl in females and 11- 12.9 g/dl in males.

Among the cases, 16% had mild anemia, 61% had moderate anemia, and 23% had severe anemia as depicted in Figure 4.

Mean HbA1c in severe anemia was 8.17±3.1, in moderate anemia was 10.88±3.1, and in mild anemia was 9.62±2.4. Severe anemia had a significantly lower HbA1c, which was statistically significant with a p value of 0.002

DISCUSSION

India has the second largest population of diabetics in the world.[10] With anemia having a higher prevalence in diabetics than in general population as mentioned previously, this study was done to analyse the profile of anemia in diabetic patients. To assess the type, severity and probable cause of anemia in diabetic patients. This could help in screening for and treating anemia at the earliest, as anemia is found to be an independent risk factor for development of diabetic complications.

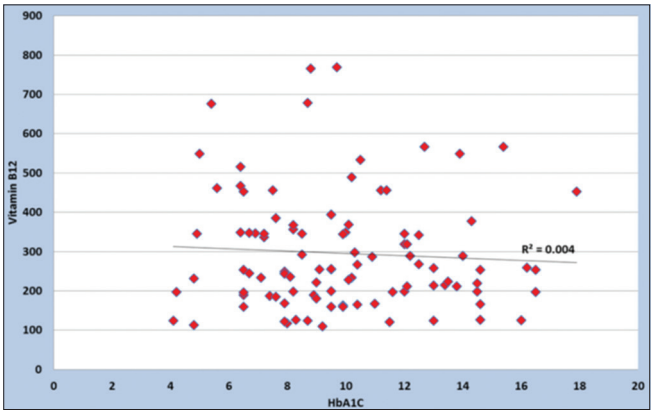

Figure 3: Scatterplot of HbA1c vs Vitamin B12

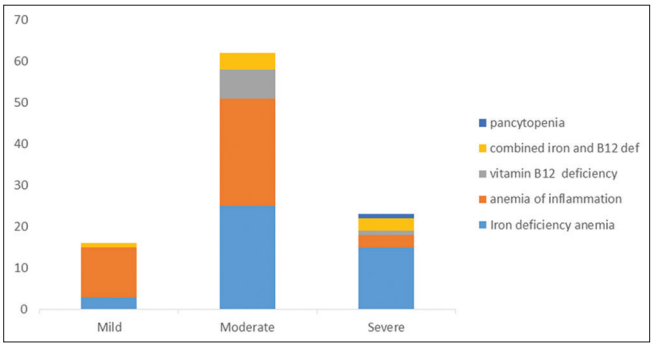

Figure 4: Proportion of patients with etiological types and severity of anemia

Mean age of the patients was 53.4±13.6 years with 49 patients being male and 51 were female. A study by Joshi et al done on general population excluding pregnant women in Madhya Pradesh showed increased prevalence of anemia in 20-39 years of age.[11]

In our study, 43% had iron deficiency anemia, 40% patients had anemia of inflammation, and 8% had vitamin B12 deficiency, 8% patients had combined iron and vitamin B12 deficiency, and 1% had pancytopenia which required further evaluation. The study by Joshi et al found microcytic hypochromic anemia to be the commonest with 55.5% prevalence, normocytic normochromic anemia with 28% prevalence and macrocytic anemia being 16.8% in general population.[11] We were unable to find other studies which investigate the prevalence of various types of anemia in diabetics with preserved renal function.

Additional causes of iron deficiency in diabetes when compared to general population are as follows, chronic hyperglycaemia promotes the modulation of transferrin receptors by glycation, which might impair the capacity of these receptors to bind iron, and thus reduce iron availability.[12] Patients with diabetes mellitus have an increased prevalence of chronic gastritis [13] and Helicobacter pylori infection[14] which hamper iron absorption. Some patients, especially type 1 diabetes also have an associated malabsorptive disorder, such as celiac disease, that reduces iron absorption.[15] Inadequate iron stores can result in decreased responsiveness of erythropoiesis to erythropoietin.[16]

Our study shows higher prevalence of AI in diabetes when compared to general population. Diabetes mellitus is a chronic inflammatory state that is characterized by increased levels of pro-inflammatory cytokines like IL-1, 1L-6, and TNF,[17] which leads to suppression and apoptosis of erythroid progenitor cells [18] and hepcidin mediated downregulation of ferroportin receptors, hence defective release of iron from stores. These also lead to reduced response to erythropoietin.[4]

Metformin, one of the most commonly used oral antidiabetic agents, has been associated with malabsorption that leads to vitamin B12 deficiency,[19] which can potentially result in megaloblastic anemia in susceptible individuals. Type 1 Diabetes is frequently associated with autoimmune gastritis and pernicious anaemia with prevalence of 5–10% and 2.6–4%, respectively, compared with 2% and 0.15–1% in the general population.[20]

Causes for unexplained anemia in diabetes are as follows- Inappropriately low erythropoietin level is an important cause of early anemia in patients with diabetes mellitus.[4] This is secondary to tubular dysfunction due to chronic hypoxia in the renal interstitium even before onset of renal dysfunction.

[3] Glitazones can precipitate anaemia, probably as a result of hemodilution secondary to fluid retention.[21] Antihypertensive medications, such as angiotensin-converting-enzyme inhibitors [22] and angiotensin II receptor blockers,[23] might adversely influence erythropoiesis and promote anaemia by inhibition of the growth of erythroid precursors.

Mean HbA1c in iron deficiency anemia was higher than other type of anemia. In the study done by Christy AL et al, to find the influence of iron deficiency anemia on HbA1c levels in diabetic individuals with controlled plasma glucose levels, they found a positive correlation between iron deficiency anemia and increased A1C levels, especially in the women.[24]

Mean HbA1c in vitamin B12 deficiency is 9.61 whereas in vitamin B12 sufficient individuals is 9.96, though p value was not significant. This result is similar to the study done by Ford et al, wherein they found that when compared with the controls, cases with a low Hb concentration and normal iron status had a significantly lower HbA1c ($P = 0.001$).[25]

Among the cases, 28% had mild anemia, 49% had moderate anemia, and 23% had severe anemia. We were unable to find any studies investigating the severity of anemia in diabetes with preserved renal function.

Severe anemia had a significantly lower HbA1c i.e 8.17 ± 3.1 compared to moderate anemia with HbA1c of 10.88 ± 3.1, and mild anemia with HbA1c of 9.62 ± 2.4, which was statistically significant with a p value of 0.002. This could be because of severe decrease in red cell mass, leading to decrease in HbA1c. This could be explained by the fact that in the presence of severe anemia, the effect of Iron deficiency anemia and vitamin B12 deficiency anemia on the HBA1c could be negligible which could open a research avenue to find cut-off of Hemoglobin below which, type of anemia would have no effect on HBA1c.

Following studies have investigated the prevalence of anemia in diabetes in the absence of nephropathy. A Cohort Study done by Craig KJ et al was published in 2005 , and they opined that, although only a small number of subjects in the group were overtly anemic i.e. 17% of males and 11.8% of females, all subjects had an ongoing, small but significant decrease in Hb since presentation. This study of diabetic patients without nephropathy also showed an expected increase in Erythropoietin production in response to lowering levels of Hb but without the expected reticulocyte response.[26] This could be indicative of erythropoietin resistance which led to increased EPO production.

A retrospective study by Mahjoub AR et al in 2015 studying the prevalence of anemia in diabetic patients with Normal renal function found the prevalence of anemia to be 22% (44 out of the 200). Out of the 44 anemic patients, 41% had anemia with normal renal function (18 out of 44). From the 18 patients with normal renal function, 5 had iron deficiency anemia and 1 had autoimmune disease, while the remaining 12 patients (27% of anemic patients) did not have any known cause of anemia. They hypothesized that; it could likely be secondary to direct glucose toxicity to erythrocyte precursors in the bone marrow or from oxidative stress to mature erythrocytes.[27]

Another case control study investigating anemia in the absence of nephropathy ,in India by Pathak J et al in 2019 opined that anemia was more prevalent in patients with Type 2 Diabetes Mellitus when compared to controls (Odds Ratio = 2.04, $P < 0.05$). On comparing the anemic cases and controls in both genders, the Odds ratio for males and females was 2.14 and 2.04 respectively with $P < 0.05$.[28]

CONCLUSION

According to our study, iron deficiency anemia was the commonest, followed by anemia of inflammation in anemic diabetic patients with preserved renal function. This was in concordance with the incidence in general population, except that the proportion of anemia of inflammation was higher. This can be explained by diabetes being a pro-inflammatory state, hence leading to higher incidence of AI than in general population. We can infer that with better control of diabetes , the pro-inflammatory state can be controlled, and in turn reduce the incidence of AI as this is an independent risk factor for progression of diabetic complications. This study highlights the need for further research in identifying, whether glycaemic control alone could improve AI or other unknown factors are playing a role in increasing the prevalence of AI in anemic diabetic patients with normal renal functions. Hence we have to identify and acknowledge the higher prevalence of AI in diabetes in the absence of renal dysfunction also.

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Author's Contribution:
VK-Concept and design of the study, collected data, prepared first draft of manuscript; **ARK-** Concept and design of the study, collected data, statistically analysed and interpreted, prepared first draft of manuscript, critical revision of the manuscript.

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