Anemia in Type 2 Diabetes Mellitus in Absence of Renal Insufficiency

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ABSTRACT

Introduction: Diabetes Mellitus is associated with many complications such as microvascular, macrovascular and non vascular. Presence of anemia in diabetes is due to the disease itself rather than usual causes of anemia. Apart from causing usual symptoms, anemia also increases the risk of cardiovascular disease in diabetics. Here, we have conducted a study to compare the presence of anemia in patients with Diabetes, with that in healthy population.

Material and Methods: A case-control study was conducted in a tertiary care hospital setting in Vadodara,Gujarat. A total of 120 patients were enrolled, of which 60 were cases who had Diabetes Mellitus type 2 and 60 were healthy controls, matched for age and gender. A detailed clinical history and examination was done for both cases and controls. Blood investigations in form of a complete hemogram, thin peripheral smear, blood sugar and serum creatinine was done. Only individuals with normal serum creatinine levels were included in the study. Comparison was done between the two groups for the presence of anemia, in absence of renal involvement.

Results: Anemia was more prevelant 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 $P < 0.05$.

Conclusion: Patients with diabetes mellitus type 2 are at a higher risk of suffering from anemia irrespective of their renal function.

Keywords: Diabetes, Anemia, Hemoglobin

INTRODUCTION

Diabetes Mellitus refers to a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. The world prevalence of Diabetes among adults (aged 20-79 years) will 6.4%, affecting 285 million adults in 2010 and will increase to 7.7% and 439 million adults by 2030. Between 2010 and 2030 there will be a 69% increase in number of adults with Diabetes in developing countries and a 20% increase in developed countries.[1] Diabetes is fast gaining the status of a potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with the disease.[2,3] The prevalence of Diabetes is predicted to double globally from 171 million in 2000 to 366 million in 2030 with a maximum increase in India.[4] It is predicted that by 2030, diabetes mellitus may inflict up to 79.4 million individuals in India.[4] India is the diabetes capital of the world with 41 million Indians having diabetes, every fifth diabetic in the world is an Indian.[2]

Diabetes is a highly disabling disease, which can cause blindness, amputations, kidney disease, anemia, cardiovascular and brain complications among others, impairing the functional capacity, autonomy and individual's quality of life.[5] Anemia represents an emerging global health problem that negatively impacts quality of life and requires an ever-greater allocation of healthcare resources.[6] The anemic framework promotes reduced exercise capacity, fatigue, anorexia, depression, cognitive dysfunction, decreased libido and other factors, which increase cardiac risk patients and depress the quality and life expectancy of the same.[7]

Diabetes is the single most common cause of end stage renal disease and therefore the most common cause of renal anemia. In additon, anemia may be more common in diabetics and develop earlier than in patients with renal impairment from other causes.[8] Anemia has been found in about 10% of patients with diabetes mellitus and normal kidney function.[9] In a cohort of > 9000 patients without renal disease, diabetes mellitus was an independent determinant of hemoglobin levels.[10] Anemia is a common complication of diabetes mellitus and an independent contributor to the pathogenesis and progression of other diabetes-related complications.[11] In addition, a number of studies have suggested that reduced hemoglobin levels may be linked to increase cardiovascular risks, hospitalization and mortality.[12] It has been observed that anemia may be present in diabetics even before the renal impairment becomes evident. Inappropriately low erythropoietin level is an important cause of early anemia in patients with diabetes mellitus.[13] Before any functional deficiency of erythropoietin is evident, however, several other factors might contribute to the development of a chronic hypoxic milieu, which promotes erythropoietic stress and potentiates the development of early anemia. These factors include diabetic nephropathy, chronic inflammation, elevated levels of advanced glycation end products, iron deficiency, antidiabetic medications, diabetic neuropathy, and low testosterone levels.[14] Here we have aimed to study

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the prevalence of anemia in diabetics, without evidence of renal insufficiency,as compared to that in healthy controls matched for age and gender.

MATERIALS AND METHODS

Study Sample: This was a Case control study carried out in the department of Medicine at Shri Sayaji General Hospital and Medical College, Baroda. The total sample size was 120, out of which 60 were cases and 60 were healthy controls, matched for age and gender. The age group kept was 40-60 years. The cases were patients diagnosed to have Diabetes Mellitus type 2 having normal serum creatinine levels. Cases were having DM for a period of atleast 1 year and not more than 5 years, diagnosed as per the WHO criteria for diagnosis of Diabetes Mellitus, i.e. HbA1c ≥6.5% or Fasting Plasma Glucose ≥126mg/dl or 2 hrs Plasma Glucose ≥200mg/dl during an Oral glucose tolerance test or in a patient with classic symptoms of hyperglycemia, a Random Plasma Glucose ≥200mg/dl.[15] In our study, for practical purposes, anemia was considered as hemoglobin <12gm/dl in males and hemoglobin levels <11gm/dl in females, as was the cutoff in the Third National Health and Nutrition Examination Survey(NHANES), where a population based study of 15,419 subjects were included from the general population of the United States.[8] The normal Serum Creatinine for males was considered as 0.6 to 1.2mg/dl and 0.5 to 1.1mg/dl in females.

The exclusion criteria for both cases and controls were patients on hematinics, associated co-morbid conditions like Congestive Heart Failure, Malignancy or any other hematological condition.

Methodology: The study received the approval from the Institutional human research and ethics committee. The cases and controls were provided with detailed written and oral information about the study and were enrolled if they willingly offered their written consent. Detailed history taking and thorough clinical examination was done following which blood samples were collected for each participant. Laboratory investigations were sent for complete hemogram, fasting and 2 hours post-prandial blood sugar and serum creatinine.

STATISTICAL ANALYSIS

Statistical analysis for the age, hemoglobin levels, serum creatinine and blood sugars was done by calculating their mean and standard deviation. A P value of less than 0.05 was considered statistically significant. Prevalence of anemia in diabetics as compared to controls was done by calculating the Odds ratio with 95% confidence interval.

RESULTS

From the 120 individuals enrolled in the study, there were 30 male and 30 female participants in both cases and controls. As shown in table 1, the mean age with standard deviation in the cases and controls was 50.52 ± 7.51 and 47.75 ± 6.93, respectively. In this study, as shown in table 2, out of the 60 cases, 23 had anemia and out of the 60 controls, 14 had

	Mean(in years)	SD
Cases	50.52	±7.51
Controls	47.75	±6.93
Table-1: Mean age		

	Cases	Controls
Anemia present	23	14
Anemia absent	37	46
Total	60	60
Table-2: Cases with anemia		

Male	Cases	Controls
Anemia present	9	5
Anemia absent	21	25
	30	30
Table-3: Proportion of anemia in male cases as well as controls		

Female	Cases	Controls
Anemia present	14	9
Anemia absent	16	21
	30	30
Table-4: Proportion of anemia in female cases as well as controls		

		Mean	SD	P value
Hemoglobin gm%	Cases	11.51	±2.03	$P<0.05$
	Controls	12.20	±1.46	
Table-5: Comparison of mean Hemoglobin levels of cases and controls vcc				

anemia. The proportion of anemia in cases is 38.33%, while the proportion of anemia in controls is 23.33%. The Odds ratio (OR) for the given data is 2.04, which indicates that the risk of anemia is 2.04 times higher in diabetic individuals than in non diabetic individuals.

Table 3 shows the proportion of anemia in male cases as well as controls. In males, 9 out of 30 cases had anemia, while amongst the controls, 5 out of 30 had anemia. The proportion of anemia in male cases was 30% and in controls was 16.66%. The Odds ratio indicates that the risk of anemia in diabetic males is 2.14 times higher than in non diabetic males

Table 4 shows the proportion of anemia in female cases as well as controls. In females, 14 out of 30 cases and 9 out of 30 controls had anemia. The proportion of anemia in female cases and controls was 46.66% and 30% respectively, the Odds ratio for which is 2.04.

Table 5 shows the comparison of mean Hemoglobin levels of cases and controls. The mean hemoglobin in cases was 11.51 ± 2.03gm/dl, while it was 12.20 ± 1.46gm/dl in the controls. The P value for hemoglobin levels in cases and controls is <0.05, which is statistically significant.

The mean serum creatinine for the cases was 0.788 ± 0.204 mg/dl. The mean fasting blood sugar and 2 hours post prandial blood sugar for the cases were 122.33 ± 2.590 mg/dl and 183.18 ± 6.571mg/dl respectively. The mean duration

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of diabetes in the cases was 3.30 ± 0.192 years.

The cases were observed to have significantly lower Hemoglobin levels, which was 11.51 ± 2.03gm/dl in comparison to controls who had Hemoglobin levels of 12.20 ± 1.46gm/dl (Odds Ratio = 2.04, P <0.05) as per Table 5.

DISCUSSION

Diabetes mellitus (DM) is a metabolic disorder of great impact worldwide.[16] Anemia, in patients of diabetes mellitus having renal insufficiency, is a common occurrence, but presence of anemia in diabetics without renal involvement has also been observed. Anemia in a diabetic person has a significant adverse effect on the quality of life and is associated with disease progression and the development of comorbidities[17], as obesity and dyslipidemia that are strongly associated with diabetic framework and significantly contribute to increasing the risk of cardiovascular disorders.[18] It is uncommon for diabetic patients to be tested specifically for anemia, till the development of nephropathy. A pan-European study was therefore undertaken by Stevens *et al.* (2003) to investigate the level of awareness and understanding of anemia among patients with diabetes.[19] They concluded that anemia has a significant impact on the quality of life of patients with diabetes and although patients are aware of anemia, their awareness of being tested for anemia is low.[19] Anemia in patients with diabetes must be treated once diagnosed, since it may contribute to the pathogenesis and progression of cardiovascular disease and serious diabetic nephropathy and retinopathy.[16]

In this study, on comparing the incidence of anemia in 60 healthy controls (23.33%) to 60 diabetics without renal insufficiency (38.33%), the odds ratio was 2.04, suggesting the risk of anemia is 2.04 times higher in diabetic individuals as compared to non diabetics. Study by Thomas MC et al reports unrecognized anemia in 23% of diabetics, this prevalence is two to three times higher than for patients with comparable renal impairment and iron stores in the general population.[12] This is consistent with NHAHES data showing an adjusted Odds ratio of 1.7 for anemia in diabetes.[8] The observation in our study is also supported by a study done by Adejumo B et al[20], where 15.3% incidence of anemia was reported in diabetics without renal involvement. Another study by Bonakdaran et al[21] reported anemia in 7.2% diabetics without renal insufficiency. A retrospective cohort study by Mahjoub AR et al suggests a high incidence of anemia with unidentified pathology in the diabetic population.[22]

In our study, in males, 9 (30%) out of 30 cases and 5 (16.66%) out of 30 controls had anemia. In females, 14 (46.66%) out of 30 cases and 9 (30%) out of 30 controls had anemia. So, the Odds Ratio in male and female sub group was 2.14 and 2.04 respectively. The mean hemoglobin level in cases and controls was 11.51 ± 2.03gm/dl and 12.20 ± 1.46gm/dl, the difference between the two being significant with a P <0.05. Anemia in patients of diabetes is known to be present in presence of renal insufficiency. Anemia may be more common in patients having diabetic nephropathy and develop earlier than in patients with renal impairment due to other causes. The commonest cause for anemia in diabetic nephropathy is found to be reduction in erythropoetin levels. Studies have found that anemia may appear early on in diabetes, even before the onset of nephropathy. This anemia is associated with the blood levels of erythropoetin that are inappropriately low for the level of haemoglobin.[23]

The high incidence of anemia may also be due to other risk factors related to DM. Several studies have reported factors that increase the risk of anemia in diabetics which include: damage to renal interstitium due to chronic hyperglycemia and consequent formation of advanced glycation end products by increased reactive oxygen species; systemic inflammation as well as reduced androgen levels induced by diabetes.[24,13] Hyperglycemia has a direct relationship with the development of an inflammatory condition showed by the increased expression of proinflammatory cytokines such as IL-6, TNF-alpha. Thus, diabetes as well as hyperglycemia due to its nature, is also an inflammatory disease character. The elevation of proinflammatory cytokines has a role in development of anemia.[21]

The limiting factor in our study was that we did not determine the type of anemia, which would have given clarity to the cause of anemia in diabetics. Also, a larger sample size would have made the results more significant.

CONCLUSION

The findings of our study suggest that the occurrence of anemia in patients of diabetes mellitus type 2 can be seen even in the absence of renal insufficiency, which is the most common cause of anemia in diabetics. Diabetics therefore, should be screened frequently for anemia, even in absence of renal involvement as anemia can lead to increased cardiovascular risk.

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