

## Original Article

### Anemia in Type 2 diabetes-Its occurrence and relationship with duration of diabetes: A pilot study

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#### Abstract:

**Introduction:** In India most diabetic patients are not investigated for anemia until appearance of clinical features of renal involvement. Also reports on relationship of duration of diabetes on the occurrence of anemia are scarce. The aims of this study were to compare the occurrence of anemia in diabetics without overt features of renal pathology with non-diabetics and to analyze the effect of duration of diabetes on severity of anemia.

**Methods:** Total 398 subjects with 205 diabetics (125 males and 80 females) and 193 (113 males and 80 females) non diabetics with controlled blood glucose, normal urea, creatinine reports, with or without hypertension were included. Duration of diabetes was noted. Haemoglobin was estimated by cyanmethemoglobin method.

**Results:** The frequency of occurrence of anemia was 46 % and 52.5 % in diabetic males and females respectively. Hemoglobin levels in males were 12.6 and 13.8 g/dl ( $p < 0.001$ ) whereas in females 11.6 and 11.9g/dl in diabetics and nondiabetics respectively ( $p > 0.05$ ). The earliest duration of diabetes which could affect hemoglobin significantly was 4 years in males and 8 years in females.

**Conclusion:** Screening for anemia in diabetics at least after 4 years of diabetes even without clinical features of renal insufficiency may improve the quality of life and moderate the progression of microvascular complications.

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#### 1. Introduction

With respect to the global prevalence the greatest absolute increase in the number of people with diabetes will be in India with a projected estimate of 79.4 millions in the year 2030 from 31.7 in 2000 (1). The prevalence of diabetes among adults in the southern states of India has been reported as being 18.6 % in urban populations and approximately 10% in rural populations (2, 3). With the prevalence rate increasing in the younger age groups (4, 5) the long term complications of diabetes can be expected to occur during their productive years causing severe economic and social burden (6).

Another chronic condition which affects the quality of life is anemia. The occurrence of anemia in diabetics was earlier attributed to renal pathology but studies have shown that anemia develops earlier in patients with diabetes when compared to patients with renal involvement due to other causes (7). Observational studies also indicate that low hemoglobin levels in diabetics may increase risk for progression of kidney disease and cardiovascular morbidity and mortality (8, 9). The Reduced hemoglobin levels independently identify diabetic patients with an increased risk of microvascular complications, cardiovascular disease and mortality. Moreover diabetics who already have reduced exertional capacity, poor wound healing or co-morbid vascular disease, anaemia constitutes an unwelcome additional burden. Correction of anemia certainly improves performance and quality of life in diabetic patients (10). In India most patients are regularly assessed for their diabetic status but they are not investigated for anemia until the appearance of clinical features of renal involvement. Studies have shown that in

selected populations, the prevalence of anemia may be higher (7). Also reports on relationship of duration of diabetes on anemia are scarce. Thus this study was done to assess the occurrence of anemia in diabetics without overt features of renal pathology who regularly attend the hospital for blood glucose estimation. It was also done to analyze the effect of duration of diabetes on severity of anemia and also if there are differences between diabetics with and without hypertension.

## 2. Materials and Methods

The study was conducted in Vydehi Institute of medical sciences, Bangalore and Sri Devaraj Urs medical college kolar, Karnataka. Blood Samples from diabetic subjects were collected by simple random sampling method from known diabetics attending diabetic clinic and medicine outpatient department. Non diabetics from the same population group were used as controls. The total sample size in the pilot study was 398 with 205 diabetics (125 males and 80 females) and 193 non diabetics (113 males and 80 females). The inclusion criteria consisted of adult type 2 Diabetic males (>20 years) with controlled hypertension or without hypertension. The subjects had their fasting and post prandial glucose, blood urea and creatinine reports within normal levels. They were not having any other overt features of renal involvement or any other complication of diabetes which was assessed by history and general physical examination. They also did not have any reports of hemoglobin estimation within the past 2-3 years. The duration since diagnosis as diabetic was noted.

Haemoglobin concentration of each sample was determined using direct measurement of cyanmethemoglobin, the conventional spectrophotometry method which is the gold standard and is used as reference for other methods (11). The cut off levels for hemoglobin was 13g/dl for males and 12g/dl for females as per WHO standards (12). The study was done with institutional ethical committee approval and informed consent of subjects. Analysis was done using SPSS -16. Significance value taken was  $p \leq 0.05$ . Independent t test was done to compare mean hemoglobin levels between diabetics and non diabetics. Chi square and Z tests were done to find significance value of occurrence of anemia between diabetics and non diabetics. One way ANOVA with post hoc Tukey HSD test and Games Howell test with multiple comparisons table was done to compare hemoglobin means between different durations of diabetes. Correlation analysis was obtained for influence of duration of diabetes and hypertension using spearman correlation and Pearson's test.

## 3. Results

Of the total 398 subjects in the study, 205 were diabetics (125 males and 80 females) and 193 non diabetics (113 males and 80 females). The mean age of diabetics was 55.87 years and that of non diabetics 47.4 years. The mean hemoglobin levels and frequency of occurrence of anemia for different levels of hemoglobin was significantly higher in diabetics than non diabetics. But when males and females were separately considered the values were not statistically significant in females (Table 1).

**Table 1.** Mean hemoglobin and frequency of occurrence of anemia in diabetics and non diabetics

		All subjects (n= 338)			Males (n= 178)			Females (n=100)		
		DM n=205	NDM n= 193	P value	DM n= 125	NDM n= 113	P value	DM n=80	NDM n=80	P value
Mean hemoglobin (g/dl)		12.337 ±1.9	13.438 ±1.7	0.000	12.635 ±1.9	13.802 ± 1.6	0.000	11.59 ±1.6	11.924 ±1.5	0.289
Occurrence of anemia for different hemoglobin levels	<13g/dl	-	-	-	57 (46%)	29 (26%)	0.001	-	-	-
	<12g/dl	75	37	0.000	34 (28%)	5 (4.4%)	0.000	41 (52.5)	32 (40%)	0.229
	<11g/dl	61	27	0.000	32 (26%)	3 (2.6%)	0.000	29 (36%)	24 (30%)	0.523
	<10g/d	22	10	0.015	12 (10%)	0 (0%)	0.001	10 (12%)	10 (12%)	1.000

Of the 205 diabetics 75 also had hypertension (43 males and 32 females) but there was not much difference in the mean hemoglobin levels between hypertensive and non hypertensive diabetics. The mean hemoglobin was of

12.6g/dl in diabetic males in both with and without hypertension and 11.4g/dl and 11.7 g/dl in diabetic females with and without hypertension respectively.

To find the earliest duration of diabetes which could cause statistically significant low mean hemoglobin levels, different combinations of duration of diabetes were formed as subgroups and multiple comparisons were done for the various combinations. Statistically significant results were obtained with the subgroup combination - up to 4 years, 4-8 years and more than eight years. The results were different for males and females. For males significant lowering of hemoglobin was seen from 4 years of duration of diabetes but for females only after 8 years (Table 2, showing trend in change of hemoglobin with duration of diabetes).

Both Pearson's and spearman's correlation tests showed a significant correlation at 0.01 level for the duration of diabetes with hemoglobin levels which indicates an increase in severity of anemia as no of years of diabetes increases.

**Table 2.** Mean hemoglobin levels with different durations of diabetes

	Mean hemoglobin g/dl			P value		
	<4 years (group1)	4-8 years (group 2)	>8 years (group 3)	Between group1&2	Between group1& 3	Between group2&3
Males	13.312±1.2	11.77±2.0	11.44±2.5	0.001	0.000	0.714
Females	11.868±1.4	12.053±1.3	10.327±1.8	0.922	0.019	0.012

#### 4. Discussions

In this study we have tried to compare the occurrence of anemia in diabetics without clinical features of renal pathology with non diabetics and also correlate the duration of diabetes with the occurrence of anemia in diabetics. In a recent Chennai based study prevalence of anemia in diabetics has been shown to 12.3 % in both males and females (13). But in this study it was much higher with 46 % and 52.5 % in diabetic males and females respectively. When compared with non diabetics the occurrence of anemia was significantly higher in diabetic males than in non diabetics (46% and 26% respectively p=0.001). In females occurrence of anemia in diabetics was not statistically significant when compared to non diabetics (52% and 40% p=0.229) even though percentage of occurrence was greater than male diabetics. The statistical non significance could be due to the fact that prevalence of anemia as such was high even in non diabetic females (40%) when compared to non diabetic males (26%). The high prevalence of anemia in females correlates with other reports as in the WHO report which gives the prevalence of anemia in South East Asian women as 41.9 to 49.4% (14). Another study on the burden of anemia in south Indian females gives the prevalence as 49.5 % (15). The WHO country office for India report on the prevalence of anemia gives the prevalence for males in India as 24% which also relates well with the finding of this study (16). Many factors have been suggested as the reason for anemia in patients with diabetes, including autonomic neuropathy (17), systemic inflammation (18), and changes in the renal tubulointerstitium disrupting the interaction between interstitial fibroblasts, capillaries and tubular cells required for normal hemopoietic function (19).

A study of diabetic patients without nephropathy showed a different picture in terms of Erythropoietin(Epo) response where the investigators had demonstrated a normal expected increase in Epo production in response to lowering levels of Hb in diabetic patients in the absence of nephropathy. This is in contrast to the characteristics of anemia associated with diabetic nephropathy where EPO deficiency is considered to be the main cause of anemia (20, 21). Another review report suggests Erythropoietin Hyporesponsivness which is defined clinically as a requirement for high doses of erythropoietin in order to raise blood Hb level in the absence of iron deficiency as a cause for anemia in diabetics. It is believed to represent impaired antiapoptotic action of erythropoietin on proerythroblasts. Possible causes of this erythropoietin hyporesponsiveness include systemic inflammation and microvascular damage in the bone marrow (22). There is also a possibility of anaemia-sensing (rather than erythropoietin secretory) mechanisms as dysfunctional at a local level in the anaemia of diabetes (7).

In the present study we found a significant correlation (p=0.01) between duration of diabetes and severity of anemia in both males and females. The earliest duration after which there is a significant fall in hemoglobin was 4 years in males (p=0.001) and 8 years in females (p=0.019). The Chennai based study reports a duration of 5 years of

diabetes as an independent predictor of anemia and their data also shows a significant variation only in males and not in females (13). One possible explanation for males having a earlier significant reduction in hemoglobin levels is that Low testosterone levels and hypogonadotropic hypogonadism are common in men with type 2 diabetes (4, 5) and more common than in the age-matched general population (6). As testosterone stimulates erythropoiesis (7) low testosterone levels may also contribute to anaemia in men with type 2 diabetes (23, 24). The results of this study show no significant differences in occurrence of anemia between hypertensive and nonhypertensive ( $p=0.67$ ) diabetics. This further substantiates the fact that diabetes can cause anemia before renal involvement whereas with hypertensives, anemia is usually associated with renal insufficiency or uncontrolled hypertension (25). In this study there is a significant correlation with age and hemoglobin levels ( $p= 0.01$ ) in both diabetics and nondiabetics which corresponds to the findings of other studies (26).

## 5. Conclusion

As per the present study anemia occurs in approximately 45-50% of diabetics and the severity significantly increases after 4 years of duration in males. As anemia is a key indicator of renal pathology and occurs early in diabetics all diabetics need to be screened for anemia at least after 4 years of diabetes even if there are no clinical features of renal insufficiency. This will improve the quality of life in diabetics and also moderate the progression of microvascular complications.

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