A study of functional erythropoietin deficiency in patients with type-2 diabetes and anemia

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Abstract— *Anemia is a common finding in diabetes, particularly in patients with diabetic nephropathy or renal impairment. This study was designed to assess the prevalence of functional erythropoietin deficiency in patients with type-2 diabetes and anemia. In a hospital based observational descriptive study, 60 diagnosed diabetic patients were included. They were divided into 2 groups: group I had diabetic patients without anemia with/without diabetic nephropathy and group II had type 2 diabetics with anemia with/without diabetic nephropathy. Most of the subjects (50%) in group I without diabetic nephropathy had their serum erythropoietin levels in the range of 15-30 IU/L with a mean value of 19.01± 2.11 IU/L. All the subjects in group I who had diabetic nephropathy had their serum EPO levels between 15-30 IU/L with a mean value 24.17±3.03 IU/L. In group II with diabetic nephropathy, most of the subjects (72.5%) had their serum EPO value <15 IU/L with a mean value of 10.45± 1.61 IU/L and all the subjects without diabetic nephropathy had their serum EPO level above 30 IU/L with mean value 36.41±3.0 IU/L. Comparison of both groups showed highly significant difference in EPO levels statistically (P<0.001). This study suggest further researches to find out relation of functional erythropoietin deficiency with a pattern of damage to the renal tubulointerstitium and microvasculature in diabetic kidney restricting the production of erythropoietin to maintain red cell mass in response to tissue hypoxia or a defect of "Anemia sensing" mechanism.*

Keywords*:* ***Anemia, Diabetes, Erythropoietin, Hemoglobin (Hb), Diabetic Nephropathy.***

I. INTRODUCTION

The world health organization (WHO) estimated that in 2014 there were 422 million patients with diabetes (mainly type 2) worldwide. Type 2 diabetes mellitus is a group of disorders characterized by hyperglycemia and associated with microvascular (optic, renal and neurological) and macrovascular (coronary and peripheral vascular) complications. Approximately 35% of patients with diabetes eventually develop nephropathy and is the leading cause of end stage renal disease. Nearly 30% of chronic renal failures in India are due to diabetic nephropathy.[1]

Anemia is a common finding in patients with diabetes and stage of CKD in patients with diabetic nephropathy than in patients without diabetes. Although a number of factors contribute to an increased prevalence of anemia in diabetes, an uncoupling of hemoglobin concentration and renal erythropoietin synthesis associated with tubular dysfunction appears to be the dominant factor.[2] The prominent damage to the cells and vasular architecture of renal interstitum, systemic inflammation, autonomic neuropathy and the induction of inhibitors of erythropoietin release have all been suggested as contributing to anemia in diabetic nephropathy[3]. This reflects the pivotal role of the kidney in the control of hemopoiesis, in sensing changes in tissue oxygenation, and subsequently in stimulating hemopoietic

precursors in the bone marrow through the production of erythropoietin by peritubular interstitial fibroblasts of the renal cortex and outer medulla.

There is a direct relationship between the severity of the anemia and the decrease in renal function. Anemia develops significantly earlier in patients with diabetes, with the Hb concentration decreasing significantly when the GFR decreases to less than 90 mL/min/1.73m^2 in men with diabetes and less than 70 mL/min/1.73m^2 in women[4]. In patients with anemia and chronic kidney disease (CKD), renal erythropoietin production is uncoupled from the Hb concentration. Instead of increasing exponentially with a decreasing Hb concentration, erythropoietin levels in patients with CKD and anemia inappropriately remain in the normal range[5]. This state may be defined as *functional erythropoietin deficiency* because erythropoietin levels conceivably could be adequate to maintain the Hb concentration in the normal range. Functional erythropoietin deficiency also appears to be a major contributor to anemia in individuals with diabetes, with and without nephropathy[6].

Therefore, the present study was designed to assess the functional erythropoietin deficiency in patients of anemia associated with type-2 diabetes, and its potential consequences for patient morbidity and mortality in diabetes.

II. METHODOLOGY

A hospital based observational descriptive type of study was conducted at SMS Medical College and Hospital, Jaipur (Rajasthan) India. Subjects who were diagnosed as type 2 diabetes mellitus were enrolled in the study. Cases who were diagnosed as type 1 diabetes and who refused to give consent were excluded. Finally, 60 eligible type 2 diabetics were enrolled in this study. All patients gave informed consent and the study protocol was approved by the ethics committee of the hospital. The patients with type-2 diabetes mellitus included in the study were grouped as:

Group I (n=20): Type -2 diabetes mellitus patients without anemia with/without diabetic nephropathy.
Group II (n=40): Patients of type-2 diabetes mellitus with anemia with/without diabetic nephropathy.

The baseline physical characteristics and investigations were compared in these two groups using statistical tests of significance.

Diabetic nephropathy was defined as having persistent albuminuria (both microalbuminuria and macro albuminuria) with albumin excretion rate (AER) > 20μg/min. Microalbuminuria being defined as two of three albumin excretion rate (AER) measurements between 20-200 μg/min and macroalbuminuria being defined as two of three AER measurements more than 200μg/min. And Anemia was defined as an Hb level < 13 gm/dl in men and <12 gm/dl in women, a sex specific definition used by WHO.

Data was analyzed by SPSS version 16 (trial version) using student chi square test and 'p' value <0.05 will be considered as significant.

III. RESULTS

Out of total 60 type 2 diabetic patients, 20 patients who didn't had anemia were included in group I and rest 40 patients who had anemia were included in group II.

The duration of diabetes in the majority of subjects in group I was between 5-10 years (50%) followed by <5 years (30%), while in group II, majority of subjects were of 11-15 years' duration (52.5%), followed by > 15 years (30%) (Table 1). The mean duration of diabetes in group I and group II was

6.65± 3.3 and 13.7 ± 0.3.03 years respectively. Both groups were comparable in terms of duration of diabetes ('p' value <0.05). Likewise both groups were comparable as per age, Fasting & PP sugar and HBA_1C level. (Table 1)

All the subjects in Group I had an estimated GFR > 60 ml/min and the mean value was 88.73±5.95 ml/min, while most of the subjects (55%) in Group II had an estimated GFR value between 30-59 ml and the mean value was 59.53±15.86 ml. On further analysis, GFR of group I was found significantly higher than group II (p value <0.01). (Table 1)

Most of the subjects in Group I with diabetic nephropathy (20%) had their serum erythropoietin levels in the range of 15-30 IU/L with a mean value of 24.17±3.03 IU/L. In group II with diabetic nephropathy, most of the subjects (72.5%) had their serum erythropoietin level <15 IU/L with mean value of 10.45± 1.61 IU/L. (Table 1).

Table 1
Comparison of different quantitative variables between both groups

S. No.	Variable	Diabetes without anemia [Group I] (N=20) (Mean ±S.D.)	Diabetes with anemia [Group II] (N40) (Mean±S.D.)	*'P' value
1	**Age (years)**	53.25±10.37	61±10.71	>0.05
2	**Duration of Diabetes (Years)**	6.65±3.34	13.7±3.03	<0.05
3	**Fasting blood glucose (mg/dl)**	156.25±43.5	173.37±47.6	>0.05
4	**Postprandial blood glucose (mg/dl)**	217.75±36.2	230.1±32.4	>0.05
5	**HbA_1C (%)**	9.31±2.05	10.39±1.88	>0.05
6	**B. urea (mg %)**	25.45±4.49	41.2±4.1	<0.01
7	**S. Creatinine (mg %)**	0.96±0.15	1.34±0.19	<0.05
8	**eGFR (ml/min)**	88.73±5.95	59.53±15.86	<0.01
9	**S.erythropoietin levels (IU/L)**	24.17±.3.03	10.45±1.61	<0.001

as per Unpaired 't' test

Majority of the subjects (50%) in group I without diabetic nephropathy had their serum erythropoietin levels in the range of 15-30 IU/L with a mean value of 19.01± 2.11 IU/L. All the subjects in group I who had diabetic nephropathy had their serum EPO level between 15-30 IU/L with a mean value 24.17±3.03 IU/L. On further analysis, no significant difference was found in distribution of cases as per various level of Serum erythropoietin (P>0.05). (Table 2).

In group II with diabetic nephropathy, most of the subjects (72.5%) had their serum EPO value <15 IU/L with mean value 10.45± 1.61 IU/L and all the subjects without diabetic nephropathy had their serum EPO level above 30 IU/L with mean value 36.41±3.0 IU/ L. On further analysis the proportion of cases with anemia were found significantly more with lower Serum erythropoietin levels (P<0.001). (Table 2).

Table 2
Comparison of various Serum erythropoietin levels in both study groups

Status of Diabetic nephropathy (DN)	Serum erythropoietin levels	Group I (N=20) (without anemia)	Group II (N=40) (with anemia)
Without Diabetic nephropathy	**<15**	6(30%)	0 (0%)
	15-30	10(50)	0 (0%)
	>30	0 (0%)	9 (22.5%)
With Diabetic nephropathy	**<15**	0 (0%)	29 (72.5%)
	15-30	4 (20%)	2 (5%)
	>30	0 (0%)	0 (10%)
*** P Value as per status of Nephropathy**		**>0.05**	**<0.001**

P value with Chi-square Test

When serum erythropoietin levels was compared in both the groups in patients who have diabetic nephropathy of both the group serum erythropoietin levels was found significatly lower in group II i.e. patients who were with anemia. (P<0.001). (Table 3)

Table 3
Serum erythropoietin levels in subjects of both groups who had diabetic nephropathy

Serum erythropoietin levels	Group I (N=20) (without anemia)	Group II (N=40) (with anemia)	Statistical significance (Group I v/s Group II)
<15	0(0%)	29 (72.5%)	***<0.001**
15-30	4(20%)	0 (0%)	
Mean ±S.D.	24.17±3.03	10.45±1.61	****<0.001**

P value with Chi-square Test** ****P value with Unpaired 't' Test

IV. DISCUSSION

In this present study, majority of the subjects (50%) in group I without diabetic nephropathy had their serum erythropoietin level in the range of 15-30 IU/L with a mean value of 19.01±2.11 IU/L. As these patients had normal renal function (normoalbuminuria) and normal Hb concentration, this level was used to define the normal range for patients in this study. In group I who had diabetic nephropathy had their serum erythropoietin level between 15-30 IU/L; with a mean value of 24.17±3.0. IU/L.

In Group II most of the subjects (72.5%) with diabetic nephropathy had their serum erythropoietin value <15 IU/L with mean value of 10.45± 1.61 IU/L and all the subjects without diabetic nephropathy had their serum erythropoietin level above 30 IU/L in Group II with mean value of 36.9 ± 3.05 IU/L.

In Group I who had diabetic nephropathy without anemia (24.17±3.03 IU/L) and Group II who had diabetic nephropathy with anemia (10.45± 1.61 IU/L), the difference between serum erythropoietin levels in two groups was statistically highly significant.

Anemia is a common complication of chronic kidney disease (CKD)[7]. The anemia of CKD is not normally observed until the GFR drop to <20-40ml/min which is equivalent to a serum creatinine of greater than 2mg/dl. The mechanism that may contribute to this anemia include shortened red cell survival, decreased erythropoietin production, blood loss because of defective platelet function and impaired erythropoiesis secondary to inhibitor or toxic metabolites. The major explanation however, is a relative erythropoietin deficiency to maintain red cell mass in response to tissue hypoxia.

Diabetes is associated with a common pattern of interstitial fibrosis and nephron drop-out that ultimately characterizes advanced CKD of any cause.[3] However, similar to anemia, tubule-interstitial damage in diabetes also may be seen, independent to and in advance of late changes of decreasing GFR.

Anemia is associated strongly with an increased risk of diabetic complications including nephropathy, retinopathy, and heart failure. Although a number of factors contribute to an increased prevalence of anemia in diabetes, an uncoupling of hemoglobin concentration and renal erythropoietin synthesis associated with tubular dysfunction appears to be the dominant factor.[2]

In some patients with diabetes and anemia, the renal capacity to produce erythropoietin is not simply abolished because the erythropoietin response to hypoxia may be preserved, even though erythropoietin levels are inappropriately low for their degree of anemia.[8] This finding, together with the fact that erythropoietin levels remain in the normal range in most patients with diabetes and anemia, suggests that erythropoietin synthesis and release pathways are not simply lost in the diabetic kidney, but rather are uncoupled from changes in the Hb concentration. This uncoupling of the Hb erythropoietin–feedback mechanism may be considered phenomenological similar to impaired glucose sensing in diabetic islets, which may respond normally to acute stimulation with arginine or tolbutamide,[9] but inappropriately to a chronic hyperglycemia.

In diabetic nephropathy, there is impaired function of erythropoietin producing fibroblasts associated with intestinal fibrosis and a defect of "Anemia Sensing" mechanism.[2]

V. CONCLUSION

The functional erythropoietin deficiency and resulting anemia is more common in patients with diabetic nephropathy than diabetic patients without diabetic nephropathy. This may be because of failure of the kidney to produce erythropoietin in response to a falling Hb is a key component of anemia in diabetes. So further researches are suggested whether duartion of DM, poor glycemic control etc in developing diabetic nephropathy and anemia. The anemia of diabetic nephropathy seems to develop in patients with type -2 diabetes before the onset of advanced renal failure and even with relatively normal levels of serum creatinine. It's also a subject to further study.

CONFLICT OF INTEREST

None declared till now.

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