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Anemia and Kidney Dysfunction in Type 2 Diabetic Patients

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Abstract

Background and Aims: The combination of diabetes and chronic kidney disease (CKD) has become a major health problem. Observational studies indicate that low hemoglobin levels in diabetics may increase risk for progression of kidney disease and cardiovascular morbidity and mortality. The aim of this work was to determine kidney dysfunction and hemoglobin level among type 2 diabetic patients.

Methods: This study included 307 patients, 169 (55%) of them were males, on the day of referral their age was 47±11 range 22 –74 years and their duration of diabetes mellitus ranged from 6-206 (mean 55±52) months. Estimated glomerular filtration rate (eGFR) by MDRD and CKD-EPI is expressed in ml/min per 1.73 m2. Anemia was defined as hemoglobin < 12 g/dl in females and < 13 g/dl in males.

Results: Prevalence of anemia was 39% of the patients, eGFR was 58 ± 25 ml/min/1.73m^2, body mass index (BMI) was 28±7 kg/m^2 mean hemoglobin for all patients was 12±2. There was a significant decrease in hemoglobin level in stage 3 CKD in comparison to stage1 and stage 2. Also there was a significant decrease in hemoglobin level in stage 4 in comparison to stage 1, 2, and 3. We found significant lower eGFR in anemic group 43±20 as compared to nonanemic group 68±22ml/min/1.73m^2. Additionally, there was significant lower hemoglobin, hematocrite and eGFR in uncontrolled diabetic patients compared with the controlled ones.

Conclusions: Anemia is prevalent among diabetics but remains under-recognized and under-treated. Therefore, we recommend screening of anemia in diabetics even at normal eGFR, and aggressive management of diabetic anemia so as to improve quality of life and outcome for the affected patients. Further studies are recommended to determine a different hemoglobin target in diabetic patients.

Keywords: Anemia, Glomerular Filtration Rate, Kidney Function Outcome

Introduction

Chronic kidney disease (CKD) and type 2 diabetes mellitus are increasing in frequency among western populations; both are potent risk factors for the development of anemia. The presence of CKD and diabetes together represent the most important combination for the development of anemia. New evidence has highlighted some of the underlying mechanisms which make diabetic patients more susceptible to dyserythropoiesis, particularly when they have developed concomitant CKD (1). Anemia is common among patients with diabetes and CKD and greatly contributes to patient outcome. Observational studies indicate that low Hb levels in such patients may increase risk for progression of kidney disease and cardiovascular morbidity

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and mortality (2). Anemia in diabetic patients with CKD is due to iron and erythropoietin deficiencies and hypo responsiveness to the actions of erythropoietin, as well as folate and B12 deficiency (3). Additionally, the combination of diabetes and CKD has become a major health problem. Accelerated cardiovascular disease in patients with diabetic nephropathy results in many patients dying before requiring renal replacement therapy (RRT). Cardiovascular disease is the most common cause of death in patients with diabetes and CKD; anemia appears to be a risk factor for mortality among these patients. Anemia prevalence is up to 10- fold higher among diabetic patients with CKD and heart failure and is a modifiable risk factor among diabetic patients (3).

Diabetes is the leading cause of kidney disease and kidney failure in the United States. Anemia is often more severe and occurs at an earlier stage of CKD in individuals with diabetes compared with those with other causes of CKD. Furthermore, diabetes is a known risk factor for coronary artery disease and small vessel disease and may be a contributing factor to the development of left ventricular hypertrophy (LVH). The combination of anemia and CKD therefore may be particularly harmful in individuals with diabetes, who already have reduced oxygen supply and increased oxygen demand (4).

It is not confirmed whether anemia directly contributes to the acceleration of complications in diabetic nephropathy or to the progression of diabetic small vessel disease. Nevertheless, patients with diabetes may be more vulnerable to the effects of anemia, since many also have significant cardiovascular disease and hypoxia-induced organ damage (5).

The aim of this study was to determine kidney dysfunction and hemoglobin level among type 2 diabetic patients at the time of their referral to both nephrology and diabetic clinic in El-Minia University hospital, Egypt.

Materials and Methods

This cross-sectional study included three hundred and seven patients with type 2 diabetes mellitus who were referred to either nephrology or diabetes mellitus clinic, internal medicine department, El-Minia University Hospital, Egypt between June 2008 and January 2010, 169 (55%) of them were males, their age on the day of referral was 47±11 range 22 –74 years and inclusion criteria were patients with type 2 diabetes mellitus. Participants were considered to have diabetes when they reported the use of insulin or oral hypoglycemic medications or when they had a fasting serum glucose level ≥ 126 mg/dl, thereby meeting American Diabetes Association criteria for the diagnosis of diabetes (6). Patients were classified to controlled and uncontrolled diabetics according to American Diabetes Association that recommends the HbA1c to be below 7% (7).

History of diabetes mellitus in all patients ranged from 6-206 (mean 55±52) months. Exclusion criteria included cigarette smokers, patients with history of recent blood loss, current or previous history of cytotoxic therapy, current or previous erythropoietin therapy, current or recent intravenous iron therapy, recent history of blood transfusion, patients on renal replacement therapy, patients with acute renal failure and patients with current history of malignancy including hematological malignancies and so a total number of 35 patients were excluded from the study.

After giving verbal consent to participate, their personal data and family history of diabetes mellitus and cardiovascular disease, duration and onset of diabetes, as well as their antidiabetic, antihypertensive and anti dyslipidemic drugs were obtained. Body waist (cm), at the level of the umbilicus with the patient standing and breathing normally, and hip circumferences (cm), at the level of the largest projection of the buttocks, were obtained by tape measure. Body weight (kg) and height (meter) in light clothes

without shoes were measured also for participants and body mass index (BMI) was calculated with the following formula:

$$BMI=\text{weight (kg)}/\text{height (m}^2\text{)}$$

Venous blood sample was drawn after complete aseptic technique for laboratory evaluation of fasting blood glucose, glycosylated hemoglobin, blood urea nitrogen (BUN), creatinine, serum albumin, total cholesterol and triglycerides, using an automated clinical chemistry dimension ES and complete blood count using an automated cell counter Sysmex NE.

GFR was estimated by MDRD (8) and CKD-EPI (9) and it was expressed in ml/min per 1.73 m^2. Anemia was defined as hemoglobin < 12 g/dl in females and < 13 g/dl in males (10, 11). CKD was defined on the basis of the Kidney Disease Outcomes and Quality Initiative guidelines (K/DOQI), which use both GFR and the presence of markers of kidney damage such as proteinuria to define CKD. K/ DOQI of the National Kidney Foundation has elaborated a classification CKD based on GFR. The guidelines also recommend that patients should be assigned to one of five stages based on the level of GFR stage 1 ≥ 90 ml/min/1.73m^2, stage 2 (60-89) ml/min/1.73m^2, stage 3 (30-59) ml/min/1.73m^2, stage 4 (15-29) ml/min/1.73m^2, stage 5 < 15 ml/min/1.73m^2 (12). Blood pressure was measured as we previously described (13).

Statistics

Data collected from patients were analyzed using an IBM compatible PC and SPSS program for windows release 13 for statistical analysis. Data were presented as mean ± standard deviation, Probability (p value) less than 0.05 was considered as statistically significant. Quantitative variables were compared using unpaired t test and one way ANOVA test.

Results

Three hundred and seven diabetic patients were referred to either nephrology or diabetes mellitus clinic, internal medicine department, El-Minia University Hospital, Egypt, at referral their mean age was 47±11, 55% were men and the mean eGFR was 58±25 ml/min/1.73m^2, body mass index (BMI) was 28±7 kg/m^2 and mean hemoglobin at referral for all patients was 12±2. Among these 307 patients, mono antidiabetic therapy was prescribed for 215 patients (70%) while 90 (29%) patients were using two drugs, and two patients (7%) were going on three drugs. No patient on erythropoietin was referred to the diabetic-renal clinic.

Table 1 of the results shows clinical and biochemical characteristics of all patients as well the stages of CKD and hemoglobin level at every stage. There was a significant decrease (p=0.001) in hemoglobin level in stage 3 in comparison to stage 1 and stage 2, also there was a significant decrease (P=0.001) in hemoglobin level in stage 4 in comparison to stage 1, 2 and 3.

Table 2 shows comparison between anemic and non anemic groups of type 2 diabetic patients. We found significant difference (P=0.001) of BUN and serum creatinine in anemic group 32±16 mg/dl, 1.9±0.8 mg/dl as compared to nonanemic group 20±3, and 1.2±0.3 mg/dl respectively. Also significant difference (P=0.001) was found in eGFR, history of diabetes and glycosyalted hemoglobin level between anemic and non anemic. Table 2 also shows comparison between controlled and uncontrolled diabetic patients. There was a significant increase (P=0.001) in the history of diabetes mellitus (71±55 months) in uncontrolled diabetics versus controlled diabetics (21±15 months). Additionally, there is a significant decrease (P=0.001) in hemoglobin, hematocrit and eGFR in uncontrolled diabetic patients in comparison to the controlled diabetic patients.

Table 1. Clinical and biochemical characteristics of all patients and at different CKD stages

parameter	All patients	Stage 1 CKD	Stage 2 CKD	Stage 3 CKD	Stage 4 CKD
Number of patients	307	31 (10%)	109 (36%)	138 (45%)	29 (9%)
Age (years)	47±11	43±9	47±9	48±11*	43±17
Males	169 (55%)	21 (68%)	68 (62%)	60 (43%)	20 (69%)
Females	138 (45%)	10 (32%)	41 (38%)	78 (57%)	9 (31%)
Weight (Kg)	80±20	78±14	80±18	82±21	69±12*†
Height (meter)	1.7±0.1	1.7±0.1	1.7±0.1	1.7±0.1	1.7±0.1
BMI (Kg m^2)	28±7	27±5	28±6	29±7	24±4*†
Body waist in (cm)	102±19	99±16	103±19	105±21	92±14*†
Hip Circumference (cm)	115±19	110±17	115±17	117±21	103±17*†
SBP (mmHg)	150±19	151±15	153±22	148±20	144±9#
DBP (mmHg)	81±13	82±10	83±13	78±14#	84±9†
MAP (mmHg)	104±14	105±10	106±15	102±15#	104±6
Total antidiabetics	1.3±0.5	1.2±0.4	1.4±0.5*	1.3±0.5	1.1±0.4#
Metformin	88 (29%)	16 (52%)	35 (32%)	33 (24%)	4 (14%)
Insulin	137 (45%)	5 (16%)	47 (43%)	71 (51%)	14 (48%)
Rosiglitazone	54 (18%)	10 (32%)	20 (18%)	20 (14%)	4 (14%)
Sulphonylurea	122 (40%)	5 (16%)	49 (45%)	57 (41%)	11 (40%)
Statin use	145 (47%)	12 (39%)	45 (41%)	79 (57%)	9 (31%)
Fasting blood glucose	139±24	121±9	126±8	144±20*#	188±15*#†
Serum creatinine (mg/dl)	1.5±0.7	0.8±0.1	1.1±0.1*	1.6±0.4*#	3±0.7*#†
BUN (mg/dl)	25±13	15±10	20±6*	27±9*#	44±23*#†
Serum Albumin (g/dl)	3.3±0.3	3.5±0.3	3.4±0.3	3.3±0.3	3.1±0.4
Hemoglobin (g/dl)	12±2	14±1	14±1	12±2*#	9±1*#†
Hematocrite (%)	37±6	42±4	41±3.5	36±1*#	28±4*#†
Glycosylated hemoglobin (%)	8±2	5.5±0.8	7±1.6*	8.9±1.8*#	11.3±2.1*#†
Cholesterol (mg/dl)	199±41	202±42	190±34	206±47#	196±20
Triglycerides (mg/dl)	186±60	194±67	172±42	198±73#	175±11
History of Diabetes (month)	55±52	8±2	20±7*	68±32*#	175±28*#†
eGFR MDRD (ml/min/1.73m^2)	53±22	95±16	64±9*	40±8*#	23±6*#†
eGFR CKD-EPI (ml/ min1.73m^2)	58±25	108±18	71±8*	44±9*#	23±3*#†

SBP, Systolic blood pressure; **DBP,** Diastolic blood pressure; **MAP,** Mean arterial blood pressure; **BUN,** Blood urea nitrogen; **eGFR,** estimated glomerular filtration rate.

* Significant versus stage I

Significant versus stage II

† Significant versus stage III

Table 3 shows comparison between patients using angiotensin converting enzyme inhibitors (ACEi) and those not using ACEi. We found significant (P=0.004) lower hemoglobin level and significant (P=0.005) lower eGFR in patients not using ACEi(Figures 1-4).

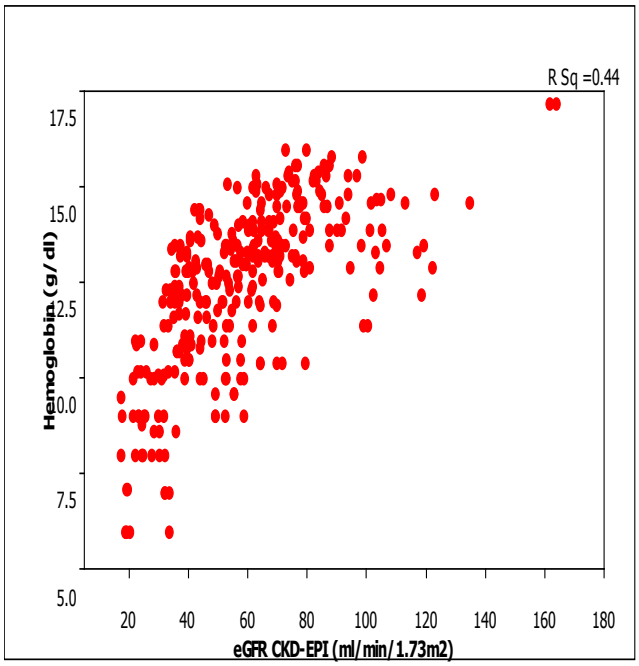

Figure 1. Relationship between hemoglobin and eGFR at referral

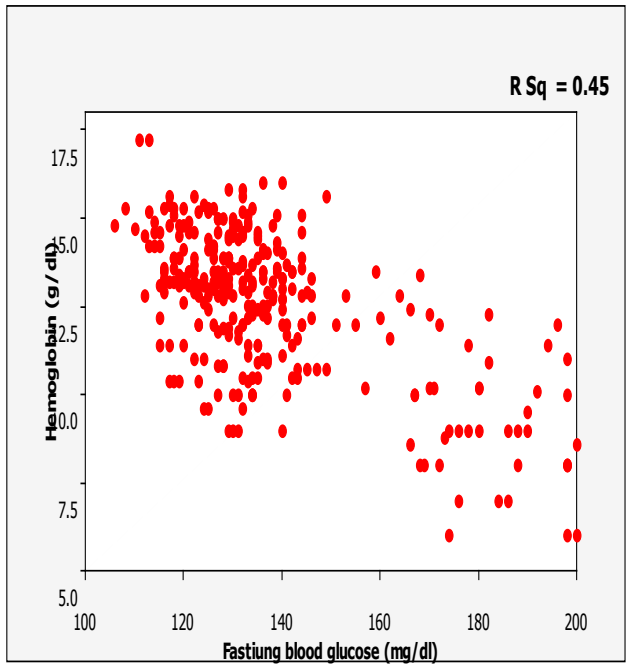

Figure 3. Relationship between hemoglobin and fasting blood glucose

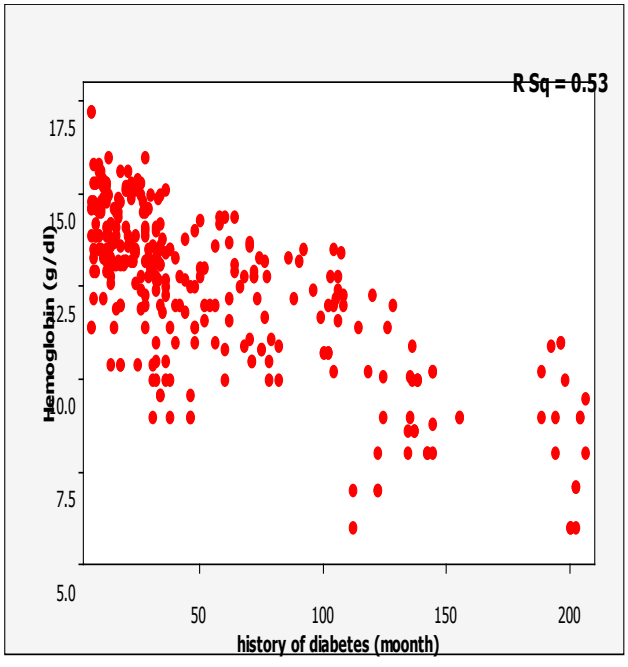

Figure 2. Relationship between hemoglobin and history of diabetes

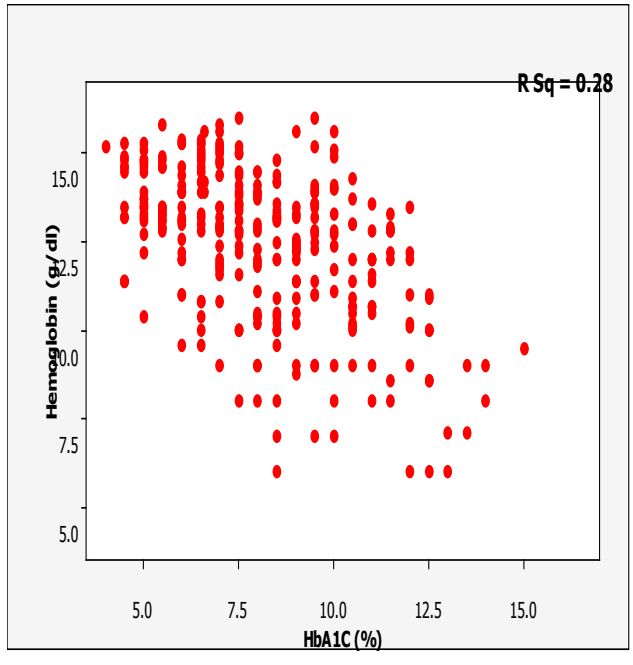

Figure 4. Relationship between hemoglobin and HbA1C

Table 2. Comparison between controlled and uncontrolled diabetics, anemic and non anemic patients

parameter	Controlled diabetics	Uncontrolled diabetics	P value	anemic	non anemic	P value
Number of patients	98 (32%)	209 (68%)		119 (39%)	188 (61%)	
Age (years)	47±10	46±12	0.4	47±13	47±10	1.00
Males	61 (62%)	108 (52%)	0.3	62 (52%)	107 (57%)	0.60
Females	37 (38%)	101 (48%)	0.2	57 (48%)	81 (43%)	0.60
Weight (Kg)	81±19	79±20	0.4	76±20	82±19*	0.01
Height (meter)	1.7±0.1	1.7±0.1	1.00	1.7±0.1	1.7±0.1	1.00
BMI (Kg m^2)	28±6	28±7	1.00	27±7	29±7*	0.02
Body waist in (cm)	104±19	102±20	0.4	100±20	104±19	0.08
Hip Circumference (cm)	116±18	114±20	0.4	112±21	116±18	0.08
SBP (mmHg)	151±21	149±19	0.4	148±17	151±21	0.20
DBP (mmHg)	82±12	81±14	0.5	77±12	83±13*	0.001
MAP (mmHg)	105±14	103±14	0.2	101±11	106±15*	0.001
Total antidiabetics	1.4±0.5	1.3±0.5	0.1	1.3±0.5	1.3±0.5	1.00
Metformin	40 (41%)	48 (23%)	0.4	27 (23%)	61 (32%)	0.10
Insulin	39 (40%)	98 (47%)	0.4	56 (47%)	81 (43%)	0.70
Rosiglitazone	24 (24%)	30 (14%)	0.07	14 (12%)	40 (21%)	0.07
Sulphonylurea	30 (31%)	92 (52%)	0.06	52 (44%)	70 (37%)	0.40
Statin use	37 (38%)	108 (52%)	0.08	53 (45%)	92 (49%)	0.60
Fasting blood glucose	123±8	47±25*	0.001	155±29	129±11*	0.001
Serum creatinine (mg/dl)	1.1±0.3	1.7±0.1*	0.001	1.9±0.8	1.2±0.3*	0.001
BUN (mg/dl)	20±8	27±14*	0.001	32±16	20±8*	0.001
Serum Albumin (g/dl)	3.4±0.3	3.3±0.3*	0.007	3.2±0.3	3.5±0.3*	0.001
Hemoglobin (g/dl)	13.6±1.5	11.9±2.2*	0.001	10.3±1.6	13.8±1*	0.001
Hematocrite (%)	40±4	36±4*	0.001	32±5	41±3*	0.001
Glycosylated hemoglobin (%)	5.6±0.7	9.3±1.8*	0.001	9.3±2.3	7.3±1.9*	0.001
Cholesterol (mg/dl)	196±40	200±41	0.4	198±45	200±38	0.70
Triglycerides (mg/dl)	184±57	187±61	0.4	188±64	185±57	0.70
History of Diabetes (month)	21±15	71±55*	0.001	94±59	30±24*	0.001
eGFR MDRD (ml/min/1.73m^2)	70±21	45±17*	0.001	38±17	62±19*	0.001
eGFR CKD-EPI (ml/min1.73m^2)	78±23	49±19*	0.001	43±20	68±22*	0.001

SBP, Systolic blood pressure; **DBP,** Diastolic blood pressure; **MAP,** Mean arterial blood pressure; **BUN**, Blood urea nitrogen; **eGFR,** estimated glomerular filtration rate.

* P< 0.05

Table 3. Comparison between patients using and not using ACE inhibitors

	Patients using ACEi	Patients not using ACEi	P value
Number of patients	150 (49%)	157 (51%)	
Age (years)	47±10	46±12	0.4
Males	91 (61%)	78 (50%)	0.2
Females	59 (39%)	79 (50%)	0.2
Weight (Kg)	81±19	78±20	0.2
Height (meter)	1.7±0.1	1.7±0.1	1.00
BMI (Kg m^2)	28±6	28±7	1.00
Body waist in (cm)	103±19	102±20	0.7
Hip Circumference (cm)	115±18	114±20	0.6
SBP (mmHg)	147±20	152±18*	0.02
DBP (mmHg)	80±12	82±14	0.2
MAP (mmHg)	102±13	105±14	0.05
Total antidiabetics	1.3±0.5	1.3±0.5	1.00
Metformin	41 (27%)	47 (30%)	0.7
Insulin	67 (45%)	70 (45%)	1.00
Rosiglitazone	26 (17%)	28 (18%)	1.00
Sulphonylurea	61 (41%)	61 (39%)	0.8
Statin use	82 (55%)	63 (40%)	0.7
Fasting blood glucose	136±21	143±26	0.01
Serum creatinine (mg/dl)	1.4±0.5	1.6±0.8	0.01
BUN (mg/dl)	24±11	26±14	0.2
Serum Albumin (g/dl)	3.4±0.3	3.3±0.4	0.012
Hemoglobin (g/dl)	12.8±1.7	12.1±2.5*	0.004
Hematocrite (%)	38±4.5	37±7	0.1
Glycosylated hemoglobin (%)	7.8±2.3	8.4±2.2	0.02
Cholesterol (mg/dl)	204±35	195±45	0.05
Triglycerides (mg/dl)	188±57	185±63	0.6
History of Diabetes (month)	46±41	64±59	0.002
eGFR MDRD (ml/min/1.73m^2)	57±24	49±19*	0.001
eGFR CKD-EPI (ml/min1.73m^2)	62±27	54±22*	0.005

ACEi, Angiotensin converting enzyme inhibitors; **SBP,** Systolic blood pressure; **DBP,** Diastolic blood pressure; **MAP,** Mean arterial blood pressure; **BUN,** Blood urea nitrogen; **eGFR,** estimated glomerular filtration rate.

* P< 0.05

Discussion

This study focused on the problem of anemia in patients with type2 diabetes mellitus and our data confirms that anemia is a significant problem at the time of referral of diabetic patients either to nephrology or diabetes mellitus clinic. Anemia was prevalent in diabetics (39%) and diabetic patients with anemia had the lowest kidney function compared with patients without anemia eGFR 43±20 versus 68±22 (P=0.001). This finding is perhaps, the first report in El-Minia Governorate diabetic population. This is in agreement with the results of Bosman (14) and Ishimura (15) who reported that diabetics are more anemic than other patients with chronic renal failure with a given eGFR. It has been suggested that erythropoietin synthesizing cells in the renal interstitium are more severely affected by diabetic nephropathy and do not respond to anemia and hypoxia (16). Therefore, there is both loss of, and resistance to erythropoietin.

Most new frontiers in the management of type 2 diabetes mellitus are aimed at achieving optimal blood glucose control so as to prevent macro- and micro-vascular complications. (17-20). The findings of the present study not only highlight the importance of meticulous management of diabetes mellitus and its importance in the outcome of anemia and kidney function (table 2) but also, it focuses on the need for routine screening of anemia in diabetic patients in nephrology and diabetic clinic.

Al-Khoury et al (21) reported a mean difference of approximately 1 g/d l at each CKD stage. The most powerful predictors of hemoglobin were diabetes mellitus and renal function. Indeed, the presence of diabetes conferred a four-fold increased risk of being anemic. Diabetes was independently correlated with anemia in a large group of patients with renal disease. This is in agreement with our results table (2).

ACEi impair erythropoiesis and promote anemia (22). The finding of lower hemoglobin in diabetic patients could have been due to: relative deficiency of erythropoietin in patients with diabetes (14), autonomic neuropathy associated with diabetes interfering with anemia sensing by the erythropoietin-producing cells in the kidney (23), a lower baseline level but appropriate erythropoietin response to hypoxia in patients with diabetic autonomic neuropathy (24), damage to the erythropoietin- producing peri-tubular fibroblasts in patients with diabetes (25), and finally, chronic inflammation associated with diabetes (26). In our results (table 5) 49% of our patients were using ACEi. Surprisingly we found that hemoglobin level and eGFR are significantly better in patients using ACEi and this may be attributed to their shorter history of diabetes mellitus and its better control as suggested by the results of glycosylated hemoglobin. Additionally, they had significant lower systolic blood pressure than those not using ACEi.

Ezenwaka et al (27) reported that the diabetic patients with anemia had significantly higher serum creatinine levels (1.4±0.1 vs. 1.0±0.03 mg/dl, $p < 0.001$ and lower GFR (67.1±3.0 vs 87.9±5.4 ml/min per 1.73 m^2, $p < 0.001$) than diabetic patients without anemia. Similarly, diabetic patients with anemia had significantly higher levels of glycated hemoglobin (index of blood glucose control). This is in agreement with our results (table 3).

Diabetic patients referred late to the nephrology clinic have limited options available to slow progression of renal disease and usually have established renal specific complications. They may need to start renal replacement therapy (RRT) with temporary access, and may not have the possibility of pre-emptive transplantation. There is no consensus as to the optimal time of referral to renal services. Some propose referral when eGFR is <30 ml/min/1.73m^2, while others feel that this may be too late to have an impact on disease progression. Late referral to a nephrology clinic is associated with a poorer outcome on RRT, loss of opportunity to slow progression of

renal disease and under treatment of renal-specific complications, in particular renal anemia (28).

Conclusions

Anemia, whether as a complication of diabetes mellitus, or as a potential risk for progression to diabetic complications, remains under-evaluated, under-recognized and under-treated. We therefore recommend early screening, even at normal eGFR, and more aggressive management of diabetic anemia with a view to improve the quality of life and ultimate outcome for the affected patients. Further studies are recommended to determine if we should use a different and perhaps better hemoglobin target in diabetic patients.

Conflict of Interest

None declared.

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