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The Incidence of Anemia and the Impact of Poor Glycemic Control in Type-2 Diabetic Patients with Renal Insufficiency

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ABSTRACT

Background: Anemia is a common finding in patients with diabetes and renal insufficiency but the effect of poor glycemic control in such patients is not clearly defined.
Aim: To determine the impact of poor glycemic control in the incidence of anemia in type-2 diabetic patients with renal insufficiency.
Methods: This cross-sectional study was conducted in 2012 and comprised 72 type-2 diabetic patients and 32 non-diabetic controls recruited from diabetes clinics of the Igbinedion University Teaching Hospital, Okada, Edo state, Nigeria. Patients were divided into groups according to glycemic control and renal function. Serum creatinine, hemoglobin concentration, blood glucose and glycated hemoglobin of subjects were measured. The presence of anemia was defined by hemoglobin level <13.0 g/dL in men and <12.0 g/dL in women. Renal insufficiency was defined as serum creatinine level >1.5 mg/dL.
Results: Incidence of anemia in the study population was 27%. Diabetic patients with poor glycemic control had greater odds (OR = 3.71; 95% CI, 1.09 – 12.56) for anemia compared to those with good glycemic control irrespective of renal function. Furthermore, patients with poor glycemic control and renal insufficiency were at a greater risk of anemia compared to those with normal renal function (OR = 5.78; 95% CI, 1.34 – 24.92).
Conclusion: Higher incidence of anemia is associated with poor glycemic control especially in diabetic patients with renal insufficiency.
Keywords: Anemia, Type-2 diabetes mellitus, Glycemic control, Renal insufficiency

1. Introduction

Anemia is the most common blood disorder and a common finding in patients with diabetes [1]. It is also considered as a key indicator of chronic kidney disease and an important cardiovascular risk factor [2, 3]. Previous studies have shown that the incidence of anemia in diabetic patients is mostly associated with the presence of renal insufficiency. Thus, patients with diabetes have a greater degree of anemia for their level of renal impairment than non-diabetic patients presenting with other causes of renal failure [1-5]. Poor glycemic control is one of the factors that have been implicated in the increased risk of anemia amongst diabetic patients with normal renal function in this population [6] and increased risk of cardiovascular disease amongst diabetic patients in other populations [7].

Limited information exists on the prevalence of anemia in diabetic patients with renal insufficiency in Nigeria. In addition, no previous studies from this population, to the best of our knowledge, have assessed the importance of glycemic control in this group of diabetic patients. We believe that a reduction of blood glucose levels and the

targeting of acceptable glycated haemoglobin levels would help reduce the risk of anemia in the diabetic population with (detected or undetected) renal dysfunction. This may be important especially at the primary care setting where routine laboratory investigations are infrequent and haematological tests are not usually included as part of the laboratory tests for the patients' management.

The present study therefore aimed at examinining the relationship of anemia with diabetes and kidney function, and to determine whether this relationship differed between patients with good glycemic control and those with poor glycemic control.

2. METHODS

Subjects

This cross sectional study comprised 106 subjects (74 type-2 diabetic patients and 32 non-diabetics). The diabetic patients were recruited from January to December 2012 and from diabetes clinics of the Igbinedion University Teaching Hospital, Okada, Edo state, Nigeria. Diabetes was diagnosed by participant's self-report, and glycated hemoglobin values >6.5%. The diabetic patients were divided into groups according to: (a) glycemic control [patients with glycemic control (n = 30) and those with poor glycemic control (n = 44)] (b) renal function (patients with normal renal function, n = 34 and patients with renal insufficiency, n = 40). Patients with good glycemic control comprised those whose glycated hemoglobin concentration (HbA1c) was ≤7.5%. The poorly controlled diabetic comprised those whose HbA1c level was >7.5%. The apparently healthy non-diabetic subjects were recruited from the same environment as the diabetic patients. Each volunteer underwent compulsory fasting blood glucose and glycated hemoglobin tests. Subjects with fasting blood glucose level >125 mg/dl and glycated hemoglobin measurement > 6.5% were excluded from the non-diabetic subjects data. The non diabetic group was further divided according to their renal functions (non-diabetic with normal renal function, n = 20; and those with renal insufficiency, n = 12). Group designation, patients' demographics and clinical features are listed in Table1.

Protocol

To be included in the study all patients had to be 18 years of age or older. Exclusion criteria included those who had history of unstable cardiovascular and peripheral diseases; those with chronic illnesses; those with recent blood loss or donated blood recently; those who have hemolytic anemia or genetic differences in the hemoglobin molecule (hemoglobinopathy) such as sickle-cell disease and other systemic disorders that could result in anemia. Blood were collected from the subjects after obtaining permission from the hospital authority, and under aseptic conditions using fresh needles and syringes and sterile containers. Blood samples were collected into floride oxalate and EDTA bottles for serum creatinine, hematocrit, hemoglobin concentration, fasting blood glucose (FBG), and glycated hemoglobin measurements respectively. The presence of anemia was defined by a hemoglobin level <13.0 g/dL in men and <12.0 g/dL in women based on definition of World Health Organization (WHO) [8]. Renal function was considered insufficient if serum creatinine values were >1.5 mg/dL for men and >1.3 mg/dL for women [9]. Fasting blood glucose was estimated using the glucose oxidase method (Randox, United Kingdom). Glycated hemoglobin A1C was assessed by ion exchange chromatography method (DIALAB, Gieselhaft, Germany). The Research and Ethics Committees of the institution approved the study and all the subjects gave their written informed consent prior to the study.

3. RESULTS

Table 1. Demographic and clinical characteristics of subjects

Variables	**Non-diabetics (n= 32) vs. Diabetics (n=74)**	**Patients with good glycemic control (n=30) vs. Patients with poor glycemic control (n=44)**	**Diabetics with normal renal function (n=34) vs. Diabetics with renal insufficiency (n=40)**
Age (yrs)	36.28 ± 11.53*** vs. 45.44 ± 11.99	37.13 ± 9.89*** vs. 51.11 ± 9.85	45.50 ± 11.60 vs. 45.40 ± 12.46
Sex (M/F Ratio)	19/13 vs. 38/36	13/17 vs. 25/19	20/14 vs. 18/22
HbA1c (%)	5.73 ± 0.45*** vs. 10.33 ± 4.59	5.95 ± 0.48*** vs. 13.32 ± 3.65	9.94 ± 5.33 vs. 10.67 ± 3.89
FBG (mg/dl)	77.22 ± 10.15*** vs. 147.01 ± 58.36	86.30 ± 15.66*** vs. 188.41 ± 35.94	128.64 ± 58.95* vs. 162.62 ± 53.77
SCr (mg/dl)	1.49 ± 1.12** vs. 2.49 ± 1.89	1.53 ± 0.88*** vs. 3.05 ± 2.14	0.92 ± 0.24*** vs. 3.72 ± 1.70
Hemoglobin (g/dl)	13.22 ± 0.92** vs. 12.35 ± 1.33	12.95 ± 0.94*** vs. 11.94 ± 1.41	12.81 ± 0.90** vs. 11.95 ± 1.51
Hematocrit (%)	41.78 ± 4.70** vs. 38.40 ± 6.80	41.0 ± 4.56** vs. 36.63 ± 7.52	41.26 ± 4.80*** vs. 35.97 ± 7.34

Abreviations: HbA1c = Glycated hemoglobin concentration; FBG = Fasting blood glucose; SCr = Serum creatinine; *P < 0.05; **P < 0.01; ***P < 0.001. Data are means ± standard deviations.

Demographic and clinical characteristics of patients are as shown in **Table 1**. Mean hemoglobin as well as the mean hematocrit values were significantly higher in non-diabetics compared to diabetics ($P < 0.01$); also in persons with good glycemic control compared to persons with poor glycemic control ($P < 0.001$ and $P < 0.01$) and in diabetic patients with normal renal function compared to those with renal insufficiency ($P < 0.01$ and $P < 0.001$) respectively. Significantly higher serum creatinine was noted in diabetics compared to non-diabetics and in patients with poor glycemic control compared to those with good glycemic control ($P < 0.01$ and $p < 0.001$) respectively. Mean HbA1c did not differ between diabetic patients with normal renal function and those with renal insufficiency. On the other hand, fasting blood glucose was significantly higher ($P < 0.05$) in diabetics with renal insufficiency compared to those with normal renal function.

The incidence of anemia in the study population (n = 106) was 21.7% (n = 23). Of the 74 diabetic patients who participated in the stduy, 27% (n = 20) had anemia. Patients with diabetes had significantly more anemia compared to the non-diabetic patients (18.9% vs. 2.8%; $P<0.001$). Chi-square test indicated significant ($X^2 = 12.56$; $p = 0.000$) difference in the incidence of anemia between non-diabetics and diabetic patients. Logistic regression further revealed that those who are diabetic are at greater risk of anemia compared to non-diabetics (OR = 3.58; 95% CI, 1.0 – 13.06).

Table 2. Incidence of anemia in diabetic patients according to renal function

	DIABETICS WITH NORMAL RENAL FUNCTION N (%)	**DIABETICS WITH RENAL INSUFFICIENCY N (%)**	**TOTAL N (%)**	**X^2**	**P-VALUE**
No Anemia	30 (40.5)	24 (32.5)	54(73.0)	7.4	0.006
Anemia	4 (5.4)	16 (21.6)	20(27.0)		
Total	34 (45.9)	40 (54.1)	74 (100)		

Among the diabetic patients, 45.9% had normal renal function, while 54.1% had evidence of renal insufficiency (**Table 2**). Patients with renal insufficiency had significantly greater incidence of anemia than those with normal renal function (21.6% vs. 5.4%; P = 0.007). Furthermore, a significant association was observed between prevalence of anemia and renal function (X^2 = 7.4; P < 0.01). Diabetic patients with renal insufficiency were more likely to develop anemia compared to those with normal renal function (OR = 5.0; 95% CI, 1.47 -16.93).

Table 3. Incidence of anemia in diabetic patients according to glycemic control status

	GOOD GLYCEMIC CONTROL N (%)	**POOR GLYCEMIC CONTROL N (%)**	**TOTAL N (%)**	**X^2**	**P-VALUE**
No Anemia	26 (35.1)	28 (37.9)	54(73.0)	4.79	0.03
Anemia	4 (5.4)	16 (21.6)	20(27.0)		
Total	30 (40.5)	44 (59.5)	74 (100)		

Among the 74 diabetic patients, 40.5% (n = 30) had good glycemic control and 59.5% (n = 44) had poor glycemic control (**Table 3**). Those with poorly controlled diabetes had significantly higher incidence of anemia than those with good glycemic control (21.6% vs. 5.4%; P = 0.007). Greater risk of anemia was also observed in those with poorly controlled diabetes compared to those with good glycemic control (OR = 3.71; 95% CI, 1.09 – 12.56).

Table 4. Incidence of anemia in diabetic patients with poor glycemic control according to renal function status.

	PGC WITH NORMAL RENAL FUNCTION N (%)	**PGC WITH RENAL INSUFFICIENCY N (%)**	**TOTAL N (%)**	**X^2**	**P-VALUE**
No Anemia	16 (36.4)	12 (27.3)	28(63.6)	6.12	0.013
Anemia	3 (6.8)	13 (29.5)	16(36.4)		
Total	19 (43.2)	25 (56.8)	44 (100)		

43.2% of diabetic patients with poor glycemic control had normal renal function, while 56.8% had renal insufficiency (**Table 4**). Significant difference was observed between the incidence of anemia in patients with poor glycemic control but normal renal function compared to those with poor glycemic control and renal insufficiency (29.5% vs. 6.8%; P = 0.01) among diabetics with normal renal function. Similarly patients with poor glycemic control and renal insufficiency were found to be at a greater risk of anemia compared to those with normal renal function (OR = 5.78; 95% CI, 1.34 – 24.92).

Table 5. Incidence of anemia in diabetic patients with renal insufficiency according to glycemic control status

	GGC WITH RENAL INSUFFICIENCY N (%)	PGC WITH RENAL INSUFFICIENCY N (%)	TOTAL N (%)	X^2	P-VALUE
No Anemia	12 (30.0)	12 (30.0)	24(60.0)	4.0	0.04
Anemia	3 (7.5)	13 (32.5)	16(40.0)		
Total	15 (37.5)	25 (62.5)	40 (100)		

Table 5 shows the incidence of anemia in diabetic patients with renal insufficiency according to glycemic control status. 62.5% of this group of patients had poor glycemic control, while 37.5% had good glycemic control. The incidence of anemia was significantly higher in patients with poor glycemic control compared to those with good glycemic control (32.5% vs. 7.5%; P = 0.01). Logistic regression also indicated that patients with poor glycemic control were at greater risk of anemia than those with good glycemic control (OR = 4.33; 95% CI, 1.01 – 19.20).

Table 6. Indices of glycemic control, renal function and anemic condition compared between diabetic patients with and without anemia

VARIABLES	NON-ANEMIC N = 54	ANEMIC N = 20	t-STAT	P-VALUE
FBG	135.61±56.44	177.80±53.22	-2.89	0.005
HbA1c (%)	7.70 ± 1.98	11.69 ± 3.82	-4.45	0.000
SCr (mg/dl)	2.03 ± 1.68	3.51 ± 2.03	-2.89	0.007
Hb (g/dl)	13.06 ± 0.58	10.43 ± 0.74	14.38	0.000
Hematocrit (%)	41.87 ± 3.21	29.05 ± 4.77	11.11	0.000

Abreviations: HbA1c = Glycated hemoglobin concentration; SCr = Serum creatinine; Hb = Hemoglobin. Data are means ± standard deviations.

Patients with anemia had significantly greater FBG, HbA1C and SCr levels compared to patients without anemia (177.80 vs. 135.61, P = 0.005; 11.69 vs. 7.70, P = 0.000 and 3.51 vs. 2.03, P = 0.007) respectively. The same trend was observed when hemoglobin and hematocrit values were compared between patients with and without anemia (**Table 6**).

Age and sex adjusted Pearson's correlation analysis indicated a significant negative associations between hemoglobin concentration and; serum creatinine level (r = -0.366; p = 0.002); fasting blood glucose (r = -0.337; p = 0.004) and glycated hemoglobin concentration (r = -0.568; p = 0.000).

4. DISCUSSION

The present study indicated a high prevalence of anemia (27%) among diabetic patients irrespective of sex, renal function and glycemic control status. Our data indicated a higher prevalence of anemia when compared to previous studies by Carwood et al (males, 11%; feamles, 16%) [10], Thomas et al (20%) [11], Craig et al (17.8%) [12], and Bonakdaran et al (19.6%) [13]. The higher incidence of anemia in our study may be due to the small sample size of our study, which also constitutes a large proportion (34%, n = 25) of patients who had poorly controlled diabetes as well as renal insufficiency. This category of diabetic patients has been shown to be more susceptible to impaired erythropoietin production and release and higher incidence of anemia [14, 15].

The presence of anemia was significantly higher in diabetic patients compared to non-diabetic subjects. Those who were diabetic were also found to be 3.5 times at greater risk of anemia than those without anemia. The present study also indicated negative correlation between hemoglobin concentration (an index for anemic

condition) and fasting blood glucose (index for diabetes). These findings strengthen previous studies which have reported higher prevalence of anemia in diabetic compared to non diabetic patients irrespective of the status of renal function [1, 2, 3, 16]. In addition, diabetic patients with renal insufficiency had more anemia and were at greater risk of anemia compared to patients with normal renal function. Negative correlations between hemoglobin concentration and serum creatinine (index of renal function) were also observed. Previous studies have associated diabetic patients who had renal insufficiency with higher prevalence of anemia compared to those with normal renal function [13, 17, 18]. Our study however is significant since it excluded those who have hemolytic anemia or genetic differences in the hemoglobin molecule (hemoglobinopathy) such as sickle-cell disease and other systemic disorders that could result in anemia.

Reducing blood glucose levels and targeting acceptable glycated haemoglobin (HbA1c) levels is the major focus in preventing the risk of micro- and macro-vascular complications [19]. Our findings indicated that irrespective of renal function, patients with poor glycemic control were at greater odds of anemia than those with good glycemic control. In patients with renal insufficiency, data indicated that those with poor glycemic control were at greater risk of anemia than those with controlled diabetes. Negative correlation was also observed between glycated hemoglobin (an index of glycemic control) and hemoglobin concentration. Previous studies in diabetic patients with normal renal function have demonstrated higher prevalence of anemia in those with uncontrolled diabetes compared to those with controlled diabetes [6, 14]. The risk of anemia in diabetics with poor glycemic control has been previously associated with diabetic autonomic neuropathy leading to impaired erythropoietin production and release [15, 20]. This condition may be worsened in poor glycemic control patients with renal insufficiency due to damage to renal achitecture produced by chronic hyperglycemia and consequent formation of advanced glycation end products [1, 2, 21] and may explain the present findings. Our study therefore underscores the importance of glycemic control in reducing the risk of anemia in the diabetic population, particularly in those with renal impairments and preventing other diabetic complications.

In conclusion, anemia is associated with poor glycemic controlparticularly in diabetic patients with renal insufficiency. This calls for the inclusion of routine hematological tests as treatment criteria for diabetes and taking into consideration the consequences of poor glycemic control and renal dysfunction, in order to make optimal therapeutic decisions for the treatment of diabetes mellitus in adults and prevent other diabetic complications.

REFERENCES

1. Thomas MC, MacIsaac RJ, Tsalamandris C, Molyneaux L, Goubina I, Fulcher G, Yue D, Jerums G. The burden of anaemia in type 2 diabetes and the role of nephropathy: a cross-sectional audit. Nephrol. Dial. Transplant 2004; 19 (7): 1792-1797.
2. Bosman DR, Winkler AS, Marsden JT, Macdougall IC, Watkins PJ. Anaemia with erythropoietin deficiency occurs early in diabetic nephropathy. Diabetes Care 2001;24(3):495-9.
3. Dikow R, Schwenger V, Schomig M, Ritz E. How should we manage anaemia in patients with diabetes? Nephrol Dial Transplant 2002;17(Suppl 1):67-72
4. Ishimura E, Nishizawa Y, Okuno S, Matsumoto N, Emoto M, Inaba M, Kawagishi T, Kim CW, Morii H. Diabetes mellitus increases the severity of anaemia in non-dialysed patients with renal failure. J Nephrol 1998;11(2):83-6
5. El-achkar TM, Ohmit SE, Mccullough PA, Crook ED, Brown WW, Grimm R, Bakris GI, Keane WF, Flack JM. Higher prevalence of anemia with diabetes mellitus in moderate kidney insufficiency: The Kidney Early Evaluation Program. Kidney International 2005; 67, 1483–1488.
6. Adejumo BI, Dimkpa U, Enwenighi CO, Onifade AA, Mokogwu AT, Erhabor TA, et al. Incidence and risk of anemia in type-2 diabetic patients in the absence of renal impairment. Health 2012; 4 (6): 304-308.
7. Ezenwaka CE, Offiah NV. Differences in glycemic control and cardiovascular risk in primary care patients with type 2 diabetes in West Indies. Clin Exp Med. 2001; **1**:91–98. doi: 10.1007/s10238-001-8018-z.
8. World Health Organization. Nutritional Anaemia. Report of a WHO scientific group. WHO, Geneva, 1968.
9. Jones CA, Mcquillan GM, Kusek JW, *et al*: Serum creatinine levels in the United States: the third National Health and Nutrition Examination Survey (NHANES III). Am J Kid Dis 1998 32: 1–9.

10. Cawood TJ, Buckley U, Murray A, et al. Prevalence of anaemia in patients with diabetes mellitus. Ir J Med Sci 2006;175:25-7.
11. Thomas MC, Cooper ME, Tsalamandris C, Maclsaac R, Jerums G. Anemia with impaired erythropoietin response in diabetic patients. Arch Intern Med 2005;165:466-9.
12. Griag K, Williams JD, Riley SG, Smith H, Owen DR, Worthing D, Cavill I, Philips AO. Anemia and diabetes in the absence of nephropathy. Diabetes care, 2005;28:1118-23.
13. Bonakdaran S, Gharebaghi M, Vahedian M. Prevalence of anemia in type-2 diabetes and role of renal involvement. Saudi J Kidney Dis Transpl, 2011; 22 (2): 286-290.
14. Kojima, K., Totsuka, Y. Anemia due to reduced serum erythropoietin concentration in non-uremic diabetic patients. Diabetes Res Clin Pract, 1995; 27(3), 229-33.
15. Ahmed, A.M., Hussein, A., Ahmed, N.H. Diabetic autonomic neuropathy. Saudi Med J, 2000; 21, 1034-7.
16. Astor BC, Muntner P, Levin A, Eustace JA, Coresh J. Association of kidney function with anaemia: the Third National Health and Nutrition Examination Survey (1988-94). Arch Intern Med 2002;162:1401-8.
17. El-achkar, T.M., Ohmit, S.E., Mccullough, P.A., Crook, E.D., Brown, W.W., Grimm, R., Bakris, G.I., Keane, W.F., Flack, J.M. Higher prevalence of anemia with diabetes mellitus in moderate kidney insufficiency: The Kidney Early Evaluation Program. Kidney International 2005; 67, 1483–1488.
18. Li Vecchi M, Fuiano G, Francesco M, et al. Prevalence and severity of anaemia in patients with type 2 diabetic nephropathy and different degrees of chronic renal insufficiency. Nephron Clin Prac 2007;105:62-7.
19. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood glucose control with metformin on complication in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998; 352:854–865.
20. Toyry, J.P., Niskanen, L.K., Mantyseari, M.J., Lansimies, E.A., Uusitupa, M.I. Occurrence, predictors and clinical significance of autonomic neuropathy in NIDDM. Ten year follow-up from the diagnosis. Diabetes, 1996; 45, 308-315.
21. Schuster, S.J., Koury, S.T., Bohrer, M., et al. Cellular sites of extrarenal and renal erythropoietin production in anaemic rats. Br J Haematol, 1992; 81, 153–159.