Association of Anemia with Cardiovascular disease in patients with Diabetic Nephropathy with normal GFR

[1]Dr. Khurshid Ahmad Khan,M.D. [2]Professor Javed Akram M.D.

Allama Iqbal Medical College & Jinnah Hospital Lahore

University of Health Sciences Lahore & Higher Education Commission of Pakistan

1)

Dr. Khurshid Ahmad Khan

M.D. (USA), F.A.C.E.(USA),D.A.B.I.M. (USA),

D.A.B.I.M. in Diabetes and Endocrinolgy (USA).

Associate Professor of Medicine & Endocrinology

Allama Iqbal Medical College/JHL

University of Health Sciences/HEC

2)

Professor Javed Akram

M.D. (USA), MRCP (UK), FRCP (London)

FRCP (Glasgow), FRCP (Ed.), FACP (USA),

FACC (USA), FASIM (USA)

Principal and Chief Executive Officer

Allama Iqbal Medical College/JHL

For Correspondence:

Dr. Khurshid Ahmad Khan

M.D. (USA), F.A.C.E.(USA),D.A.B.I.M. (USA),

D.A.B.I.M. in Diabetes and Endocrinolgy (USA).

Associate Professor of Medicine & Endocrinology

Allama Iqbal Medical College/JHL

University of Health Sciences/HEC

Lahore   Pakistan

Telephone… 092-3002026000

E. mail… Dockhan@Live.com

Abstract:

Background: Anemia is recognized as an independent cardiovascular disease (CVD) risk factor in diabetic patients with end stage renal disease. However, it is not known whether anemia associated with early diabetic nephropathy increases CVD risk.

Objective: To assess the effect of anemia on CVD risk in patients with Stage 1 chronic kidney disease (CKD).

Materials and Methods: Cross sectional analysis of 2,502 diabetic patients with stage 1 CKD. Demographic, clinical and laboratory data were collected from two teaching hospitals affiliated with medical university in Lahore, Pakistan.

Results: Of the 2,502 diabetic patients examined, 96% had type 2 diabetes. Age (years) = 64.2 ± 0.2, BMI= 29.6 ± 0.2, duration of diabetes (years) = 9.3 ± 0.17, Hemoglobin A1C (A1C) % =7.8 ± 0.04. Males represented 83.2% of the cohort.

The CVD group included 909 (36.3%) of the total cohort and had a significantly lower mean serum hemoglobin (g/dl) (12.9±0.05 Vs 13.4±0.04, p <0.01), and hematocrit (%) (38.8±0.19 Vs 40.04±0.17, p<0.01), compared to those without CVD events. Both groups had stage I diabetic nephropathy with urinary albumin >30 mg/gm creatinine and normal GFR (>90 ml/min/1.73m^2). Using the National Kidney Foundation (NKF) threshold Hb of 12 g/dl for initiation of work up for anemia in chronic kidney disease, in our logistic regression model the odds ration (OR) for CVD in patients with Hb<12 g/dl was 1.94 (95% CI= 1.6-2.3, p <0.01). After adjusting for CVD risk factors, anemia remained a significant predictor for CVD events OR=1.64 (95%CI = 1.3-2.0, p<0.01). We also examined Hb as a continuous variable and found that; for each unit decrease in hemoglobin, the odds of CVD increases, OR =1.21 (1.14-1.28, p <0.01)

Conclusion: Our data suggest that anemia associated with early diabetic nephropathy is an independent risk factor for CVD. Further studies are needed to validate our findings and to determine the mechanisms of increased CVD associated with anemia in early nephropathy.

Introduction

CVD is the major cause of morbidity and mortality in patients with diabetes mellitus (DM), accounting for up to 80% of excess mortality in this patient population (1). The pathophysiology of CVD in diabetes involves traditional and novel cardiac risk factors, including hypertension, dyslipidemia, smoking, hyperglycemia, insulin resistance/ hyperinsulinemia, oxidative stress, inflammation, endothelial dysfunction and hypercoagulability (2). In addition, the presence of microalbuminuria is an independent

risk factor for CVD (2). CVD is prevalent in patients with chronic kidney disease CKD (3). These patients are more likely to die than to progress to end stage renal disease (ESRD) (3,4). CVD events and death is substantially increased (by 20-40%) in patients with CKD and DM compared to those with CKD due to other causes (5,6). Therefore, prevention of CVD morbidity and mortality in this vulnerable population is of paramount importance. Data indicates that control of traditional CVD risk factors is largely sub-optimal in patients with diabetes (7,8). Therefore identification of potentially modifiable CVD risk factors in diabetic patients is of great importance. Anemia is a potentially modifiable candidate risk factor for CVD (9-17) that is common in patients with diabetes particularly those with albuminuria or reduced renal function and often goes unrecognized and untreated (18,19). Data from the Third National Health and Nutrition Examination Survey (NHANES III) showed that the prevalence of anemia is increased in people with diabetes even with preserved renal function (20). While GFR and iron stores are the strongest predictor of Hb level in diabetic patients, they do not explain the increased prevalence of anemia in this patient population (18). Therefore, other factors such as deficiency and/or impaired action of erythropoietin, inflammation and oxidative stress may contribute to the development of anemia in diabetes and may explain in part the increased prevalence of CVD.

Anemia and CKD are well documented independent risk factors for CVD in vulnerable populations such as diabetic patients, the elderly and those with underlying heart disease (21-27). There are number of potential reasons for this relationship. First, the cardiac response to chronic anemia includes increases in heart rate, cardiac index, and output as well as expansion of plasma volume (28). These hemodynamic adaptations

result in left ventricular hypertrophy and remodeling, increased sympathetic activity and reduced effective cardiac index, all associated with increased CVD morbidity and mortality. Studies have demonstrated an independent association between hemoglobin level and LV mass in CKD patients (9,21). Levine et al (9), reported that patients with CKD had a 32% increase in left ventricular mass index (LVMI) for each gram decrease in hemoglobin. Portoles et al (29), reported that partial correction of the hematocrit from 26 to 35% in CKD patients was associated with 17% reduction in LVMI and Hayashi et al found that increasing the hematocrit from 27% to 47% was associated with 21% reduction over baseline LVMI (11). Furthermore, erythropoietin deficiency and resistance in CKD may also increase CVD, as it has direct cardiac effects (30,31). Other risk factors include increased peripheral and myocardial hypoxia, increased inflammatory cytokines and oxidative stress. Further, decreased progenitor cell availability and consequent reduction in endothelial repair likely contribute to increased CVD associated with anemia (32-34).

Anemia is a common finding in early diabetic nephropathy, compared to that in non-diabetic nephropathy with a similar degree of renal impairment (35). Furthermore, treatment of anemia decreases CVD risk in the diabetic population with advanced renal disease, for example: in diabetic renal transplant patients, increasing hematocrit has been observed to reduce early post-transplant CVD risk (36). Studies have shown beneficial effect of anemia treatment with erythropoietin on CVD morbidity and mortality (37). However, data on anemia and CVD in patients with early diabetic nephropathy (stage 1 CKD) is scarce. Therefore, we aimed to assess the association of anemia and CVD in early diabetic nephropathy

Materials and Methods:

Prior to the conduct of the study, Institutional Review Board approval was obtained at each participating center. This is a cross sectional analysis of 2,502 diabetic patients admitted on medical floors of two different medical institutions in Lahore, Pakistan. Both hospitals were university affiliated medical centers. Diabetic patients without the diagnosis of chronic kidney disease were identified by diagnostic billing codes. Records of all patients who qualified were examined and demographic, clinical and laboratory data were collected. Patients were selected for the study if they had GFR >90 ml/min/1.73m^2 and urinary albumin > 30 mg/gm creatinine.

Statistical analysis:

Data were analyzed in a two-step process, first univariate methods were used for comparison of CVD groups (CVD and non CVD) such as t-test for continuous variables and Chi square analysis for categorical variables. Then we used multivariate logistic regression models to estimate the odds ratio (OR), for CVD events in patients with anemia, defined as hemoglobin <12 gm/dl, before and after adjusting for other CVD risk factors including age, sex, BMI, smoking, hypertension, HDL-cholesterol, total cholesterol, hemoglobin A1c, glomerular filtration rate (GFR) and urine albumin.

Results:

Demographic and clinical laboratory characteristics of patients with and without CVD events are shown (table1). Of the 2,502 diabetic patients examined, 96% had type 2

diabetes. Age (years) = 64.2 ± 0.2, BMI= 29.6±0.2, duration of diabetes (years) = 9.3± 0.17, Hemoglobin A1C (A1C) % =7.8±0.04. Males represented 83.2% of the total cohort. The CVD group included 909 (36.3%) of the total cohort and had a significantly lower mean serum hemoglobin (g/dl) (12.9±0.05 Vs 13.4±0.04, p <0.01), and hematocrit (%) (38.8±0.19 Vs 40.04±0.17, p<0.01), compared to those without CVD events (table 2). Both groups had stage I diabetic nephropathy with urinary albumin >30 mg/gm creatinine and normal GFR (>90 ml/min/1.73m^2). We used the definition for stage 1 nephropathy, given by the National Kidney Foundation/ Kidney Disease Outcomes Quality Initiative (NKF K/DOQI), as kidney damage with normal or increased GFR (38). There was no significant difference in the level of urinary albumin between the 2 groups (table 2). GFR was significantly lower in the group with CVD compared to those without CVD (table 2). Using the National Kidney Foundation (NKF) threshold hemoglobin value of 12 g/dl for initiation of work up for anemia in chronic kidney disease (38), in our logistic regression model the odds ration (OR) for CVD in patients with HB<12 g/dl was 1.94 (95% CI= 1.6-2.3, p <0.01). After adjusting for CVD risk factors, anemia remained a significant predictor for CVD events OR=1.64 (95%CI = 1.3-2.0, p<0.01).

When we examined hemoglobin as a continuous variable, we found that; for each gram/dl decrease in hemoglobin, the odds of CVD increases, OR =1.21 (1.14-1.28).

We also divided the cohort into 2 groups according to the hemtocrit value (table 3), and found that, the OR for CVD significantly increases (P<0.01), comparing the group with the hemtocrit of <37% to those above 37%, (OR =1.89 (1.57-2.28) (95% CI). After adjustment for CVD risk factors including age, sex, family history, body mass index, duration of diabetes, cigarette smoking, hypertension, HDL-cholesterol, total cholesterol,

hemoglobin A1c, glomerular filtration rate and urine albumin, the effect of decreasing hemtocrit on CVD risk remains significant with OR for CVD being significantly higher in those with hematocrit <37%, compared with those above 37%, OR 1.53 (1,3-2.0), P<0.01. Furthermore, we examined the hematocrit as a continuous variable and found that with each % decrease in hematocrit, the odds CVD increases, OR= 1.057 (1.036-1.079).

In order to assess the effect of aspirin on anemia, we assessed the interaction between aspirin and hemoglobin in the 2 groups (CVD Vs non-CVD) (table4), using general linear model, univariate analysis and we found that aspirin use had no effect on hemoglobin concentration P= 0.664

Conclusion:

Our data suggests that anemia associated with stage 1 CKD increases CVD risk. In fact, with slightest drop in hemoglobin, above the currently recommended level for work up and treatment in patients with kidney disease (38), CVD risk was substantially increased. Possible explanation for our findings is the presence of erythropoietin deficiency that has been increasingly recognized to occur earlier in patients with diabetes compared to non-diabetic patients with the same level of renal impairment (35). In fact a recent report suggests that erythropoietin deficiency may precede the onset of overt nephropathy in diabetic patients (40). Furthermore, accumulating evidence indicates that erythropoietin therapy is associated with decreased inflammation, oxidative stress (21) and CVD morbidity and mortality in patients with ESRD treated with peritoneal dialysis (21) as well as those treated with HD. Therefore, studies are needed to characterize the anemia in

patients with stage 1 CKD, in terms of its association with erythropoietin deficiency and increased cardiovascular and inflammatory markers. This is crucial to elucidate the cause of increased CVD events in these patients in order to develop appropriate preventive strategies. Our data suggest that the lower hemoglobin in the CVD group is likely to be secondary to early nephropathy since GFR in this group was significantly lower than that of the non-CVD patients. This is consistent with the accumulating data indicating that erythropoietin deficiency precedes the onset of anemia and nephropathy in patients with type 2 diabetes (40). Further studies are also needed to determine whether treatment of anemia in these patients would result in decrease in the surrogate markers of CVD that could serve as a basis for randomized controlled trials to assess whether treatment of anemia in early diabetic nephropathy would result in decreased CVD events and cause specific mortality.

References:

1) Grundy SM, Benjamin IJ, Burke GL, et al. Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. Circulation 1999; 100:1134-46.

2) McFarlane SI, Banerji M, Sowers JR. Insulin resistance and cardiovascular disease. J Clin Endocrinol Metab 2001; 86:713-8.

3) Levin A, Djurdjev O, Barrett B, et al. Cardiovascular disease in patients with chronic kidney disease: getting to the heart of the matter. Am J Kidney Dis 2001; 38:1398-407.

4) Culleton BF, Larson MG, Wilson PW, Evans JC, Parfrey PS, Levy D. Cardiovascular disease and mortality in a community-based cohort with mild renal insufficiency. Kidney Int 1999; 56:2214-9.

5) Agodoa L. United States Renal Data System (USRDS). Nefrologia 2000; 20 Suppl 5:13-6.

6) Foley R. Cardiac disease in diabetic patients with renal disease. Acta Diabetol 2002; 39 Suppl 1:S9-14.

7) McFarlane SI, Jacober SJ, Winer N, et al. Control of cardiovascular risk factors in patients with diabetes and hypertension at urban academic medical centers. Diabetes Care 2002; 25:718-23

8) Saydah SH, Fradkin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. Jama 2004; 291:335-42.

9) Levin A, Singer J, Thompson CR, Ross H, Lewis M. Prevalent left ventricular hypertrophy in the predialysis population: identifying opportunities for intervention. Am J Kidney Dis 1996; 27:347-54.

10) Portoles J, Torralbo A, Martin P, Rodrigo J, Herrero JA, Barrientos A. Cardiovascular effects of recombinant human erythropoietin in predialysis patients. Am J Kidney Dis 1997; 29:541-8.

11) Hayashi T, Suzuki A, Shoji T, et al. Cardiovascular effect of normalizing the hematocrit level during erythropoietin therapy in predialysis patients with chronic renal failure. Am J Kidney Dis 2000; 35:250-6.

12) Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE. The impact of anemia on cardiomyopathy, morbidity, and and mortality in end-stage renal disease. Am J Kidney Dis 1996; 28:53-61.

13) Collins AJ, Li S, St Peter W, et al. Death, hospitalization, and economic associations among incident hemodialysis patients with hematocrit values of 36 to 39%. J Am Soc Nephrol 2001; 12:2465-73.

14) London GM, Pannier B, Guerin AP, et al. Alterations of left ventricular hypertrophy in and survival of patients receiving hemodialysis: follow-up of an interventional study. J Am Soc Nephrol 2001; 12:2759-67.

15) Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med 1998; 339:584-90.

16) Pereira AA, Sarnak MJ. Anemia as a risk factor for cardiovascular disease. Kidney Int Suppl 2003:S32-9.

17) Sarnak MJ, Tighiouart H, Manjunath G, et al. Anemia as a risk factor for cardiovascular disease in The Atherosclerosis Risk in Communities (ARIC) study. J Am Coll Cardiol 2002; 40:27-33.

18) Thomas MC, MacIsaac RJ, Tsalamandris C, Power D, Jerums G. Unrecognized anemia in patients with diabetes: a cross-sectional survey. Diabetes Care 2003; 26:1164-9.

19) Stevens PE, O'Donoghue DJ, Lameire NR. Anaemia in patients with diabetes: unrecognised, undetected and untreated? Curr Med Res Opin 2003; 19:395-401.

20) Astor BC, Muntner P, Levin A, Eustace JA, Coresh J. Association of kidney function with anemia: the Third National Health and Nutrition Examination Survey (1988-1994). Arch Intern Med 2002; 162:1401-8.

21) McFarlane SI, Salifu MO, Makaryus J, Sowers JR. Anemia and cardiovascular disease in diabetic nephropathy. Curr Diab Rep 2006; 6:213-8.

22) Sorlie PD, Garcia-Palmieri MR, Costas R, Jr., Havlik RJ. Hematocrit and risk of coronary heart disease: the Puerto Rico Health Program. Am Heart J 1981; 101:456-61.

23) Gagnon DR, Zhang TJ, Brand FN, Kannel WB. Hematocrit and the risk of cardiovascular disease--the Framingham study: a 34-year follow-up. Am Heart J 1994; 127:674-82.

24) Carter C, McGee D, Reed D, Yano K, Stemmermann G. Hematocrit and the risk of coronary heart disease: the Honolulu Heart Program. Am Heart J 1983; 105:674-9.

25) Mozaffarian D, Nye R, Levy WC. Anemia predicts mortality in severe heart failure: the prospective randomized amlodipine survival evaluation (PRAISE). J Am Coll Cardiol 2003; 41:1933-9.

26) McClellan WM, Flanders WD, Langston RD, Jurkovitz C, Presley R. Anemia and renal insufficiency are independent risk factors for death among patients with congestive heart failure admitted to community hospitals: a population-based study. J Am Soc Nephrol 2002; 13:1928-36.

27) O'Meara E, Clayton T, McEntegart MB, et al. Clinical correlates and consequences of anemia in a broad spectrum of patients with heart failure: results of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Program. Circulation 2006; 113:986-94.

28) Duke M, Abelmann WH. The hemodynamic response to chronic anemia. Circulation 1969; 39:503-15.

29) Portoles J, Torralbo A, Martin P, Rodrigo J, Herrero JA, Barrientos A. Cardiovascular effects of recombinant human erythropoietin in predialysis patients. Am J Kidney Dis 1997; 29:541-8.

30) Nissenson AR, Nimer SD, Wolcott DL. Recombinant human erythropoietin and renal anemia: molecular biology, clinical efficacy, and nervous system effects. Ann Intern Med 1991; 114:402-16.

31) Tramontano AF, Muniyappa R, Black AD, et al. Erythropoietin protects cardiac myocytes from hypoxia-induced apoptosis through an Akt-dependent pathway. Biochem Biophys Res Commun 2003; 308:990-4.

32) Andreotti F, Coluzzi G, Cecchetti S, et al. Reduced CD34+, renal anemia, and adverse outcomes. Am Heart J 2006; 152:e21.

33) Andreotti F, Coluzzi G, Lavorgna A, et al. Relation between nitric oxide metabolites and haemoglobin concentrations in patients with ischaemic heart disease. Heart 2007; 93:255-7.

34) Andreotti F, Coluzzi G, Crea F. Letter by Andreotti et al regarding article, "Hemoglobin level, chronic kidney disease, and the risks of death and hospitalization in adults with chronic heart failure: the Anemia in Chronic Heart Failure: Outcomes and Resource Utilization (ANCHOR) study". Circulation 2007; 115:e313; author reply e314.

35) Bosman DR, Winkler AS, Marsden JT, Macdougall IC, Watkins PJ. Anemia with erythropoietin deficiency occurs early in diabetic nephropathy. Diabetes Care 2001; 24:495-9.

36) Djamali A, Becker YT, Simmons WD, Johnson CA, Premasathian N, Becker BN. Increasing hematocrit reduces early posttransplant cardiovascular risk in diabetic transplant recipients. Transplantation 2003; 76:816-20.

37) Rao M, Pereira BJ. Prospective trials on anemia of chronic disease: the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT). Kidney Int Suppl 2003:S12-9.

38) K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002; 39:S1-266.

39) National Kidney Foundation/NKF K/DOQI Guidelines:http://www.kidney.org/professionals/doqi/kdoqi/p5_lab_g4.htm

40 . Nabila AA Abdella, Oluseguna A, Mojiminiyi, Walid A Aldahi. Low erythropoietin precedes the onset of anemia and nephropathy in patients with type 2 diabetes. Abstract 803-P ADA 64th scientific sessions, Orlando FL, June 4-8, 2004.

Table 1. Demographic characteristics, Cardiovascular risk factors and medication use in patients with and without cardiovascular disease

	Diabetic patients without CVD* N=1,593	Diabetic patients with CVD* N=909	P- value Significant level <0.05
Age (years) mean SEM	62±0.3	69±0.4	<0.01
% of males	39.4	60.6	<0.01
Body mass index (kg/m^2)	29.7±0.2	29.6±0.2	NS
Duration of DM (years)	8.3±0.2	10.9±0.3	<0.01
Hemoglobin A1C	7.8±0.06	7.7±0.05	NS
Percentage with hypertension	76.2	87.2	<0.01
Systolic BP (mmHg)	133±0.5	133±0.7	NS
Diastolic BP (mmHg)	74±0.3	72±0.4	NS
Total Cholesterol (mg/dl)	178±1.0	171±2.1	<0.01
LDL-cholesterol (mg/dl)	105±1.0	100±1.2	NS
HDL-cholesterol (mg/dl)	45 ±0.4	41 ±0.4	<0.01
Triglyceride (mg/dl)	152±3.4	149±3.7	0.01
Percentage of smokers	14.2	18.4	0.03
Percentage with F/H of CAD	9.6	14.8	<0.01
Percentage on Statins	44.2	68.0	<0.01
Percentage on ACE-inhibitors	52.6	60.9	<0.01
Percentage on aspirin	36.1	62.9	<0.01

*CVD = the presence of one or more of the following: coronary artery disease, angina, coronary revascularization, congestive heart failure, atrial fibrillation, stroke, transient ischemic attack and peripheral vascular disease

Table 2. Kidney functions and anemia in patients with and without cardiovascular disease (CVD) *

	Diabetic patients without CVD* N=1,593	Diabetic patients with CVD* N=909	P- value Significant level <0.05
Serum creatinine (mg/dl)	0.81±0.15	0.86±0.12	<0.01
Microalbumin (mg/24 hrs)	138.4±3.9	143.5±2.81	NS
GFR**	111±0.8	106±1.3	<0.01
Hemoglobin (g/dl)	13.4±0.04	12.9±0.05	<0.01
Hematocrit %	40.4±0.1	38.8±0.19	<0.01

*CVD = the presence of one or more of the following: coronary artery disease, angina, coronary revascularization, congestive heart failure, atrial fibrillation, stroke, transient ischemic attack and peripheral vascular disease.
** Based on MDRD formula glomerular filtration rate (GFR) was calculated as follows: Estimated GFR (ml/min/1.73m^2) = exp (5.228-1.154xln(S_{Cr})-0.203 x ln (age)- (0.299 if female) (38,39)

Table 3. Logistic regression analysis showing the odds of cardiovascular disease (CVD) before and after adjustment for CVD risk factors including age, sex, family history, body mass index, duration of diabetes, cigarette smoking, hypertension, HDL-cholesterol, total cholesterol, hemoglobin A1c, glomerular filtration rate and urine albumin. We used the National Kidney foundation hematocrit cut point of 37% and hemoglobin of 12 gm/dl for initiation of work up for anemia (24)

	Diabetic patients without CVD	Diabetic Patients with CVD	Odds Ratio (95% CI)			
			Before adjustment	P-Value	After adjustment	P-Value
Hematocrit >=37%	1213 (78.5%)	578 (65.8)	1	-------	1	------
<37%	333 (21.5%)	301 (34.2)	1.89 (1.57-2.28)	<0.01	1.53 (1.23-2.09)	<0.01
Hemoglobin >=12 gm/dl	1247 (82.4%)	621 (70.6)	1	-------	1	------
<12 gm/dl	273 (17.6 %)	259 (29.4)	1.94 (1.6-2.3)	<0.01	1.64 (1.3-2.0)	<0.01

Table4. Effect of aspirin use on anemia in patients with and without cardiovascular disease. Using a 2x2 ANOVA, the non-significant (P= .664) interaction analysis demonstrated that the effect of aspirin did produce hemoglobin concentration differences in either of the CVD categories. Means and SEM are in table below.

CVD	Aspirin	Mean hemoglobin (gm/dl)	SEM
No	No	13.51	0.057
	Yes	13.35	0.74
Yes	No	12.94	0.103
	Yes	13.0	0.073