Original Article

Anemia and Diabetic Retinopathy in Type 2 Diabetes Mellitus

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Abstract

Objectives: To estimate the prevalence of anemia in persons with type 2 diabetes mellitus and its role as a risk factor for the presence and the severity of diabetic retinopathy, in a population based study.

Methods: In all 5999 subjects from the general population aged ≥40 years were enumerated for the study. A total of 1414 persons identified with diabetes underwent comprehensive eye examination, and stereoscopic digital fundus photography was used for diabetic retinopathy grading. All patients underwent hemoglobin estimation for detection of anemia. Univariate and multivariate analyses were done to determine the independent risk factors for anemia.

Results: The prevalence of anemia (Hb <12g/dl in women and <13g/dl in men) was 12.3%. Between 40 and 49 years of age, prevalence of anemia was higher in women than in men (26.4 % vs 10.3%). Men with anemia, and not women, had 2 times the risk of developing diabetic retinopathy. Multivariate analysis revealed independent predictors for anemia: age group more than 69 years OR 2.49 (95% CI 1.44-4.30), duration of diabetes of more than 5 years OR 1.56 (1.09-2.69) and the presence of diabetic retinopathy OR 1.82 (95% CI 1.22-2.69).

Conclusion: Every tenth individual in a population of diabetes mellitus could be anemic. Identifying and treating anemia would make a great impact in managing microvascular complications such as diabetic retinopathy.

Introduction

Anemia, a common complication, is more prevalent in persons with diabetes than in persons without diabetes.[1] Anemia also develops earlier and is more severe in patients with diabetes than in patients with renal impairment from other causes.[2] The World Health Organization (WHO) guidelines recommend investigation of anemia when the Hb is less than 12g/dl in women and less than 13g/dl in men.[3] Using this definition, nearly 1 in 4 (23%) patients with type 1 or type 2 diabetes had anemia.[1] Anemia has been associated with the development and progression of both microvascular and macrovascular complications of diabetes.[1] Anemia can lead to falsely low HbA1c levels, which may result in under treatment of hyperglycemia, which in turn will contribute to the progression of both microvascular and macrovascular diabetic complications.[4]

Gender was considered as a significant influencing factor for the prevalence of anemia in the general population.[5] However, there is a paucity of data regarding gender influence on anemia in persons with diabetes and diabetes related complications. Secondly, only a few studies demonstrated the role of anemia as an independent risk factor for diabetic retinopathy, particularly in population-based studies.[6-8]

The present population-based study was conducted to find out the prevalence of anemia in persons with type-2 diabetes and also to report its influence on the presence and severity of diabetic retinopathy in men and women individually.

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Materials and Methods

Study subjects were recruited from the Sankara Nethralaya Diabetic Retinopathy Epidemiology And Molecular-genetics Study (SN-DREAMS). The study design and research methodology of SN-DREAMS 1 is described in detail elsewhere.[9] The study area was Chennai metropolis with a population of 4.3 million, distributed in 155 divisions of ten zones. In all, 5999 subjects from the general population aged ≥40 years were enumerated; multistage random sampling was stratified based on economic criteria. Of the 5999 subjects enumerated, 1414 persons identified with diabetes based on the WHO criteria [9] (both known and newly diagnosed) were analyzed for the study (96.20% response rate for first fasting blood sugar estimation, 85.60% response rate for base hospital examination, 8.7% turned out as non diabetic after second blood sugar and 0.78% of retinal images were un-gradable).The study was approved by the Institutional Review Board, and informed consent was obtained from subjects as per the Helsinki declaration.

Procedures pertaining to the present study are described below:

Diabetic Retinopathy grading

The fundi of all patients were photographed using 45° four-field stereoscopic digital photography. The diagnosis of diabetic retinopathy was based on the modified Klein classification.[10] For those who showed evidence of any retinopathy, additional 30° seven-field stereo digital pairs were taken. All photographs were graded by two independent observers in a masked fashion; the grading agreement was high (k=0.83).

Table 1 : Clinical Characteristics of Study Subjects (n=1414)

Variables	Anemia Absent n=1240 (87.7%) n (%)	Anemia Present n=174 (12.3%) n (%)	P
Gender			
Men	663 (88.4)	87 (11.6)	
Women	577 (86.9)	87(13.1)	0.391
Age Group (years)			
40-49	362 (91.9)	32 (8.1)	0.001
50-59	440 (88.4)	58 (11.6)	
60-69	309 (85.8)	51 (14.2)	
>69	129 (79.6)	33 (21.4)	
Albuminuria			
Normoalbuminuria	1017 (88.4)	133 (11.6)	0.053
Microalbuminuria	194 (85.8)	32 (14.2)	
Macroalbuminuria	29 (76.3)	9 (23.7)	
Duration of DM			
<5 years	745 (91.0)	74 (9.0)	0.001
>5 years	495 (83.2)	100 (16.8)	
Blood Pressure (BP)			
Systolic BP <140 mm of Hg	616 (87.6)	87 (12.4)	0.936
≥ 140 mm of Hg	624 (87.8)	87 (12.2)	
Diastolic BP <90 mm of Hg	848 (86.7)	130 (13.3)	
>90 mm of Hg	392 (89.9)	44 (10.1)	0.091
Diabetic Retinopathy (DR)			
Absence of DR	1036 (89.4)	123 (10.6)	< 0.001
Presence of DR	204 (80.0)	51(20.0)	
Non-Sight threatening DR	175 (81.4)	40 (18.6)	0.197
Sight threatening DR	29(63.6)	11 (27.5)	

Estimation of Hemoglobin and Microalbuminuria

Hemoglobin estimation was done using capillary method by calorimetric hemoglobinometer (Merck Micro Lab 120 semi-automated analyzer). Microalbuminuria estimation was done by a semi-quantitative procedure (Clintek 50 Bayer Urine Analyzer) using the first morning sample of urine.

Definitions

Anemia

Anemia was defined as a hemoglobin concentration of <13 g/dl in men and <12 g/dl in women.[2]

Hypertension

Hypertension was defined as the systolic blood pressure (BP) was ≥140 mm Hg or the diastolic BP was ≥ 90 mm Hg or the patient was on antihypertensive treatment.

Non- sight threatening Diabetic retinopathy

Non-sight threatening Diabetic retinopathy included cases of mild or moderate non-proliferative diabetic retinopathy.[11]

Sight threatening Diabetic retinopathy

Sight-threatening diabetic retinopathy (Referable diabetic retinopathy) was defined as severe non-proliferative diabetic retinopathy, proliferative diabetic retinopathy and clinically significant macular edema.[11]

Albuminuria

The patient was considered normo-albuminuric if Albumin Creatinine Ratio (ACR) was less than 30mg/g, micro-albuminuria if ACR was between 30–300 mg/g and macro-albuminuria if ACR was above 300 mg/g.[12]

Table 2 : Gender Specific Distribution of Variables Influencing Prevalence of Anemia (n=174)

Variables	Men n=87 (11.6%) n (%)	Women n=87 (13.1%) n (%)	P
Age group (years)			
Mean age ± SD (years)	62.84±9.33	55.82±10.26	<0.001
40-49	9 (10.3)	23 (26.4)	0.006
50-59	25 (28.7)	33 (37.9)	0.198
60-69	31 (35.6)	20 (230)	0.067
>69	22 (25.3)	11 (12.6)	0.033
Hemoglobin (g/dl)			
Mean Hb ± SD (g/dl)	11.77±1.17	11.09±0.87	<0.001
< 11	12 (13.8)	26 (29.9)	0.010
11 - 12	31 (35.6)	61 (70.1)	<0.001
12 - 13	44 (50.6)	0 (0.0)	<0.001
Albuminuria			
Normoalbuminuria	66 (75.9)	69 (77.0)	0.858
Microalbuminuria	16 (18.4)	16 (18.4)	1.000
Macroalbuminuria	5 (5.7)	4 (4.6)	0.732
Duration of DM			
<5 years	31 (35.9)	43 (49.4)	0.066
>5 years	56 (64.4)	44 (50.6)	
Blood Pressure (BP)			
Systolic BP < 140 mm of Hg	45 (51.7)	42 (48.3)	0.649
≥ 140 mm of Hg	42 (48.3)	45 (51.7)	
Diastolic BP <90 mm of Hg	72 (82.8)	58 (66.7)	0.015
>90 mm of Hg	15 (17.2)	29 (33.3)	
Diabetic Retinopathy (DR)			
Absence of DR	56 (64.4)	67 (77.0)	0.067
Presence of DR	31 (35.6)	20 (23.0)	
Non-Sight threatening DR	24 (77.4)	16 (80.0)	
Sight threatening DR	7 (22.6)	4 (20.0)	0.872

Statistical analysis

Statistical analyses were performed using the statistical software (SPSS for Windows, ver.13.0 SPSS Science, Chicago, IL). The results were expressed as mean ± SD if the variables were continuous, and as percentage, if categorical. Student t test for comparing continuous variables, and χ^2 test, to compare proportions amongst groups were used. Both univariate and multivariate logistic regression analyses were performed to study the effect of various risk factors using anemia as a dependent variable. From the univariate analysis, variables with p values ≤0.1 were included in the multivariate logistic regression analysis to derive at the parsimonious model. P value of ≤0.05 was considered significant.

Results

The mean age of the population (n=1414) was 56.32± 10.02 years; 53.0% (n = 750) were men. The prevalence of anemia was 12.3% (174 /1414); it was 11.6% (87/ 750) in men and 13.1% (87/664) in women.

Table 1 shows clinical characteristics of the study subjects with or without anemia. Presence of anemia was significantly related to increasing age, micro - and macroalbuminuria, duration of diabetes mellitus of more than 5 years, and presence of any diabetic retinopathy.

Table 2 shows gender specific prevalence of anemia and variables influencing it. Men with anemia were older than women (mean age, 62.84 vs 55.82). However, between 40 and

Table 3 : Multiple Logistic Regression Analysis of Risk Factors for Anemia

Variables	n (%)	Odds ratio (95% CI)	P
Gender			
Men	750 (53.04)	1.00	
Women	664 (46.67)	1.28 (0.92 – 1.77)	0.140
Age Group (Years)			
40-49	394 (27.86)	1.00	
50-59	498 (35.21)	1.29 (0.81-2.05)	0.276
60-69	360 (25.45)	1.57 (0.97-2.53)	0.067
>69	162 (11.45)	2.49 (1.44-4.30)	0.001
Albuminuria			
Normoalbuminuria	1150 (81.32)	1.00	
Microalbuminuria	226 (15.98)	1.01 (0.35-1.55)	0.975
Macroalbuminuria	38 (2.68)	1.45 (0.65-3.22)	0.367
Duration of DM (Years)			
<5 years	819 (57.92)	1.00	
>5 years	595 (42.07)	1.56 (1.09-2.20)	0.013
Diabetic Retinopathy (DR)			
Absence of DR	1159 (81.96)	1.00	
Presence of DR	255 (18.03)	1.82 (1.22-2.69)	0.003
Non-Sight threatening DR	215 (15.20)	1.00	
Sight threatening DR	40 (2.82)	1.66 (0.76-3.60)	0.200

49 years of age, women had higher prevalence of anemia than men (26.4% vs 10.3%); such differences were not observed after the age of 50 years.

The median levels of Hemoglobin (g/dl) were lower in women compared to men (median, 11.3 vs 12.1) (p<0.001). In women, the hemoglobin was between 11 and 12 g/dl in 70.1%, whereas in men, it was between 12 and 13 g/dl in 50.6%.

A higher prevalence of anemia was observed in women (49.4% vs 35.9%) if the duration of diabetes mellitus was less than 5 years, and the converse was true (50.6% vs 64.4%) if the duration of diabetes mellitus was more than 5 years. Diastolic blood pressure was related to anemia, only in women (p=0.001). Presence of diabetic retinopathy was related to anemia in men though statistically not significant (p=0.067). Variables not related to anemia included micro – and macro-albuminuria, systolic blood pressure, and severity of diabetic retinopathy such as sight-threatening diabetic retinopathy.

Multivariate analysis (Table 3) identifies independent risk factors related to anemia. These were individuals above the age of 69 years OR 2.49 (95% CI: 1.44-4.30), duration of diabetes mellitus of more than 5 years OR 1.56 (95% CI: 1.09–2.20), and presence of any diabetic retinopathy OR 1.82 (95% CI: 1.22-2.69). Other variables such as gender, micro- and macroalbuminuria or severity of diabetic retinopathy were not related to anemia.

Multivariate analysis was also performed with DR as dependendent variable, revealed that presence of anemia increased the risk of DR with OR 1.80 (95% CI: 1.21-2.69) times compared to those who do not have anemia (Variables were adjusted for age, gender, duration of diabetes and albuminuria)

Table 4 summarizes gender-specific, multivariate analysis. In men, significant factors were age more than 50 years, diastolic blood pressure of more than 90 mm of Hg, and presence of any diabetic retinopathy; in women, none of these factors was significant.

Table 4 : Multiple Logistic Regression Analysis of Gender specific Risk factors for Anemia

Variables	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
	Men (n=750)		Women (n=664)	
Age Group(years)				
40-49	1.00		1.00	
50-59	2.33 (1.05 – 5.15)	0.037	0.89 (0.49 – 1.59)	0.693
60-69	3.83 (1.74 – 8.42)	0.001	0.74 (0.39 -1.43)	0.397
>69	5.33 (2.30 – 12.35)	<0.001	1.21 (0.54 -2.74)	0.644
Duration of DM				
< 5 Years	1.00		1.00	
> 5 Years	1.53 (0.93-2.54)	0.096	1.58 (0.97-2.59)	0.067
Blood Pressure (BP)				
Diastolic BP < 90 mm of Hg	1.00		1.00	
Diastolic BP > 90 mm of Hg	0.53 (0.29 – 0.97)	0.040	1.10 (0.68-1.79)	0.694
Diabetic Retinopathy (DR)				
Absence of DR	1.00		1.00	
Presence of DR	2.05 (1.22 – 3.45)	0.007	1.69 (0.94 -3.02)	0.079

Discussion

The results of the present epidemiological study estimated the prevalence of anemia to be 12.3% in individuals with type 2 diabetes mellitus, above the age of 40 years; no gender differences were observed. Individuals with anemia were 1.80 times more likely to develop diabetic retinopathy than individuals with no anemia. In men, the risk of developing diabetic retinopathy increased to 2.05 times, but not in women. Quing Quio et al [6] reported odds of 2.0 for the presence of diabetic retinopathy in individuals with anemia (defined as Hb <12g/dl) in a cross sectional study of 1691 individuals with diabetes. David et al [7] in Early Treatment of Diabetic Retinopathy Study evaluated the effect of moderate levels of anemia by hematocrit measurements. They reported that in their lowest hematocrit group (defined as male <40%, female <34%), anemia was observed to be an independent risk factor with odds of 1.52 times for the development of high-risk proliferative diabetic retinopathy and of severe vision loss over a 5-year follow up. Our study, however, did not show association between anemia and sight-threatening diabetic retinopathy, possibly due to the small number in the subsets. In contrast, Quing Quio et al [6] reported odds of 5.0 for severe retinopathy with presence of anemia. Similar risk of anemia with severe retinopathy was also reported in a case series by Shorb.[8]

Detection of anemia and its treatment is important in the management of diabetic retinopathy. In those patients who had both anemia (Hb-10g/dl) and diabetes mellitus, Friedman and associates reported that treatment with erythropoietin was correlated with substantial resolution of macular hard exudates.[13] The improved hemoglobin concentration with therapy of anemia improves tissue oxygenation and may result in reduced VEGF production, which improves the hyperpermeability and reduces the stimulus for neovascularization.[13]

Gender specific analysis showed differences in variables that might be influencing anemia in both men and women. In the fifth decade of life (age, between 40-49 years), anemia was more prevalent in women than men; however, thereafter there were no differences. The possible reason could be the onset of menopausal period around this age in women. If the duration of

diabetes was less than 5 years, more women had anemia, and the converse was true if the duration was more than 5 years. Once again, the proximity to menopausal age might be influencing such differences. The degree of anemia between 11-12 g/dl was about 70% in women compared to 36% in men, while half of the men showed anemia in the range of 12-13 g/dl. Such differences in gender in particular in a population-based study have not been analyzed before.

Another salient finding was the association between the duration of diabetes and the prevalence of anemia. Individuals with duration of diabetes of more than 5 years have 1.56 times higher risk of developing anemia than those with diabetes for less than 5 years. These observations suggest that anemia evaluation should be considered in the routine management of persons with diabetes and should be treated to minimize the risk of microvascular complications such as nephropathy and retinopathy.

The strengths of present study are: it is a population based sample, using gold-standard photographic grading and analyzes gender influence on the prevalence of anemia in individuals with type 2 diabetes mellitus. On the other hand, limitation is the point estimation of risk factors, and thereby, a causal relationship between anemia and diabetic retinopathy cannot be proved. Such kind of cause and effect relationship needs longitudinal studies.

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Conflict of Interest: None

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