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Original Article

Internal Medicine Section

Prevalence of Anaemia in Patients with Type-2 Diabetes Mellitus in the Absence of Renal Impairment: A Cross-sectional Study

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ABSTRACT

Introduction: Despite an increasing incidence of diabetic nephropathy, undermining the renal production of Erythropoietin (EPO), there are significant number of studies being reported with anaemia among diabetic patients with renal insufficiency, implicating numerous theoretical pathogenesis. Its impact being ignored over the years among Indian contexts, women and men in rural Southern India are particularly vulnerable to anaemia. The associated risk factors and occurrence of anaemia in Type-2 Diabetes Mellitus (T2DM) can be seen even in the absence of renal insufficiency.

Aim: To determine the prevalence of anaemia in T2DM patients with normal renal function and assessment of its association with sociodemographic characteristics, biochemical and haematological variables.

Materials and Methods: A descriptive cross-sectional study was conducted for a period of six months from December 2018 to May 2019 on total of 150 patients with T2DM, attending the Outpatient Department, Rajarajeswari Medical College and Hospital, Bangalore, India. All the patients of either sex, aged between 18-60 years, with a duration of Diabetes Mellitus (DM) more than five years, with no renal involvement, were included in the study. All statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 20.0. The Chi-square test, Z-test was used for data analysis.

Results: Among the 150 subjects, 86 (57.3%) were classified to be anaemic, with a mean age of 53 years whereas, 64 (42.6%) were classified as non anaemics with a mean age of 50 years. The mean duration of diabetes was found to be 10.5 years among anaemics and 9.7 years among non anaemics. Compared to non anaemics subjects, drug therapy with both Oral Hypoglycaemic Agents (OHA) and insulin showed a statistically significant difference among diabetic subjects with anaemia. The high prevalence of normocytic anaemia (52.3%) suggests the importance of non renal causes of anaemia in diabetic patients.

Conclusion: Patients with T2DM have an independent risk for anaemia irrespective of renal insufficiency, posing a significant adverse effect on the quality of life and the progression of the underlying disease with high cardiovascular morbidity and mortality. Hence, management of diabetic patients should include mandatory routine haematological tests, with consideration of advancing age and poor glycaemic control.

Keywords: Cardiovascular morbidity, Diabetic nephropathy, Insulin, Microvascular complication

INTRODUCTION

With urbanisation growth, obesity, sedentary lifestyle and the longer survival rate, DM, a metabolic disorder of high impact, has an estimated projected increase to 79 million Indian diabetics by 2030 [1]. According to the global nutrition report in 2016, India ranks 170 out of 180 countries for anaemia among women, worsening in the past half-a-decade across most states and Union territories, as many as 66.4% women surveyed [2,3]. As the leading cause of End-Stage Renal Disease (ESRD), diabetes is also a risk factor for anaemia, observed during the advanced stages of diabetic nephropathy [4]. The prevalence of anaemia among patients with diabetes was found to be in the range of 14-23% through various cross-sectional studies conducted across India [4-6].

Multiple pathogenesis such as autonomic neuropathy, sympathetic denervation of the kidney, damage to the renal interstitium, systemic inflammation, nutritional deficiencies and inhibition of EPO release, have been put forth to explain the occurrence of anaemia [7]. Recent studies have shown that relatively low serum EPO is linked with anaemia in diabetics even in the absence of kidney disease [7-9].

An Iranian study reported that 7.2% of diabetics with normal renal function had anaemia in comparison to 30% with moderate renal impairment. The study also showed a significant association of cardiovascular diseases and retinopathy among diabetic patients with anaemia [7]. A cross-sectional study in Nigeria reported a 15.3% incidence of anaemia in diabetic participants without renal insufficiency. The odds were higher in participants with poorly controlled diabetes (HbA1c >7.5%) and the elderly age group than in those with controlled diabetes or age less than 60 years [10].

Since, both DM and anaemia share similar symptoms, diabetic patients with normal renal function are rarely tested for anaemia. It has a significant adverse effect on the quality of life and leads to the development of other morbid complications like ischaemic heart disease and left ventricular dysfunction [11-14].

With limited studies existing among the Indian population, the need for more cohort-based research on the incidence and demographic characteristics of anaemia in diabetic patients prior to renal impairment has become imperative [15,16]. Thus, this study aimed to determine the prevalence of anaemia in T2DM patients with normal renal function and assessment of its association with sociodemographic characteristics, biochemical and haematological variables.

MATERIALS AND METHODS

This descriptive cross-sectional study was conducted over a period of six months (December 2018 to May 2019), in the Department of Medicine at the Rajarajeswari Medical College and Hospital, Bangalore, India. This study was approved by the Institutional Ethics Committee (RRMCH-IEC/49/2018-19) and voluntary informed consent from all participants was recorded.

Inclusion criteria: Willing to give written informed consent, patients of either sex aged between 18-60 years, who presented with DM for more than five years on medication, with glycalated haemoglobin (HbA1c) level more than 6.5%, and no renal involvement, were included in the study.

Exclusion criteria: Patients with type-1 DM/secondary diabetes, liver disease (chronic hepatitis and liver cirrhosis), recent blood loss/blood transfusions/haemolytic anaemia/haemoglobinopathies, thyroid disease/nephrotic syndrome, protein-losing enteropathies, creatinine >1.3 mg/dL, concomitant use of Angiotensin Converting Enzyme (ACE) inhibitor or an angiotensin II receptor blocker which may affect the study parameters, pregnancy, patients with difficulties to understand the proposed procedures were excluded.

Sample size calculation: It was calculated by Open Epi (version 3.01), considering the prevalence of non specific outcomes of 40% based on a previous study [17], with 5% precision error, and a 95% level of reliability. A total of 150 cases with T2DM were enrolled in the study.

Study Procedure

For every consenting subject, a brief history of sociodemographic characteristics, medical conditions, risk factors or co-morbidities, lifestyle factors, diet, and habitual history were obtained. Anthropometric measurements of weight, height, waist, and hip circumferences were measured as per standardised methods. Waist-hip ratio, an indicator of abdominal visceral fat, and Body Mass Index (BMI) were calculated along with clinical examination, including a recording of vital signs. Blood pressure was measured on the right arm after five minutes of rest, in a sitting position.

Haemoglobin and other indices like Mean Corpuscular Volume (MCV), Mean Corpuscular Haemoglobin Concentration (MCHC), Total Leucocyte Count (TLC) was measured using Sysmex 1000 analyser and vitamin-B12 levels were measured through Beckman Coulter AU 480 for characterising the type of anaemia which is measured in femotolitres (fL). Microcytic (MCV <80 fL) and macrocytic (MCV >96 fL) anaemia was considered based on MCV values only and hence, MCHC was not included. Diabetes was diagnosed by the subject's recent reports of Glycated Haemoglobin (HbA1c); the cut-off was 6.5% [18]. Renal parameters were obtained by a Bio-Rad D10 analyser. Proteinuria was determined by the standardised dipstick method [19].

Definitions Considered in the Study

The presence of anaemia was defined by a haemoglobin level <13.0 g/dL in men and <12.0 g/dL among women, based on the definition of the World Health Organisation (WHO) [20]. Anaemia was considered microcytic with the MCV <80 fL and macrocytic with MCV >96 fL [21]. Fasting Blood Sugar (FBS) >100 mg/dL was considered high [14]. Serum creatinine level >1.3 mg/dL was considered to be abnormal. In this study, eGFR <60 mL/min/1.73 m^2 was considered decreased and eGFR <15 mL/min/1.73 m^2 as kidney failure [22]. Nephropathy was defined as Microalbuminuria (ACR of <300 mg/gm) or Macroalbuminuria (ACR of ≥300 mg/gm) based on the urine albumin-creatinine ratio [22]. If the patient was a smoker, pack year was calculated by multiplying the number of years the person has smoked and the number of packs of cigarettes per day [23]. Physical inactivity was defined as less than 150-300 minutes of moderate intensity aerobic physical activity, or 75-150 minutes of vigorous intensity aerobic physical activity, or a combination of moderate and vigorous intensity activity throughout the week [24].

STATISTICAL ANALYSIS

Descriptive data were presented as means and Standard Deviations (SD). Inferential statistics were used in data analysis using Z-test to find the difference between clinical and biochemical variables with haemoglobin in all patients with T2DM and Chi-square analysis was done to know the gender wise association of anaemia with diabetes. All statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 20.0. Statistical significance was set at p-value <0.05.

RESULTS

A total of 150 subjects with T2DM were included and divided into anaemic and non anaemic groups, using standardised normal ranges for males (>13 g/dL) and females (>12 g/dL). Out of 150 diabetics, 86 (57.33%) subjects were classified to be anaemic and 64 (42.67%) as non anaemic. Among the anaemic diabetics, the mean duration of DM was found to be 10.5 years, whereas it was 9.7 years in non anaemic subjects. Diastolic Blood Pressure (DBP) showed a statistically significant difference among the subjects. With regarding to drug therapy on both OHA and insulin, a significant statistical difference was seen among diabetic subjects with anaemia compared to non anaemic. For patients consuming non vegetarian diet a significant statistical difference was noted in anaemics compared to non anaemic [Table/Fig-1].

Among the diabetic subjects with anaemia (86), 45 (52.32%) were found to have normocytic anaemia (MCV 80 fL-96 fL) [Table/Fig-2].

Variables	Categories	Anaemia		z-value	p-value
		Present (86) Mean±SD	Absent (64) Mean±SD		
Age (in years)		53±8.63	50±9.42	1.99	0.04
Duration of diabetes (in years)		10.5±4.83	9.7±4.2	1.08	0.28
BMI (in kg/m^2)		27.14±4.47	27.57±4.21	-0.6	0.54
Systolic blood pressure (mm of Hg)		128±15.07	130±13.15	-0.86	0.38
Diastolic blood pressure (mm of Hg)		110±15.07	85±10.36	12.03	0.002
		n (%)	n (%)	z-value	p-value
Gender	Males	41 (47.7%)	30 (46.9%)	0.009	0.92
	Females	45 (52.3%)	34 (53.1%)	0.009	0.92
Presence of co-morbidities	Hypertension	23 (26.74%)	24 (37.5%)		
	Dyslipidemia	22 (25.5%)	15 (23.4%)		
	Tuberculosis	5 (5.81%)	2 (3.12%)		
	Epilepsy	3 (3.48%)	3 (4.68%)		
	Malignancy	2 (2.32%)	1 (1.56%))		
	Chronic heart disease	1 (1.16%)	1 (1.56%)		
	Total	56 (65.11%)	46 (71.8%)	0.675	0.5
Presence of alcoholism/smoking		30 (34.8%)	20 (31.2%)	0.41	0.48
Physical inactivity		69 (80.2%)	53 (82.8%)	0.16	0.68
Diet	Vegetarian	15 (17.4%)	13 (20.3%)	0.2	0.65
	Non-vegetarian	71 (82.6%)	51 (79.7%)	9.05	0.00001
Drug therapy for DM	Only OHA	12 (14%)	09 (14.1%)	-0.97	0.33
	OHA+Insulin	74 (86%)	55 (85.9%)	3.33	0.002
Waist-hip ratio		0.83	0.85	-0.32	0.74

[Table/Fig-1]: General characteristics of the study subjects.
SD: Standard deviation

Anaemia	No. of anaemic diabetics (n=86)	%
Normocytic	45	52.32%
Microcytic	39	45.34%
Macrocytic	2	2.32%

[Table/Fig-2]: Differentiation of anaemia.

The haematological variable that showed statistical significance was haemoglobin with a mean of 10.7 g/dL in anaemic and 14.13 g/dL in non anaemic subjects. For anaemic diabetics, the mean eGFR was found to be 99.06 mL/min/1.73 m^2 in which 21 patients had reduced eGFR and for non anaemic diabetic patients mean eGFR was 102 mL/min/1.73 m^2 with 10 subjects found to have reduced eGFR [Table/Fig-3].

Variables	Anaemia		z-value	p-value
	Present (86) Mean±SD	Absent (64) Mean±SD		
Haemoglobin (g/dL)	10.7±1.81	14.13±1.3	-13.5	**0.002**
Red cells (10^6 cells/mm^3)	5.19±10.09	5.5±10.18	-0.18	0.85
Fasting blood sugar (mg/dL)	172.7±95.8	197±84.7	-1.65	0.09
Post-prandial blood sugar (mg/dL)	265.6±125.07	283.5±119.92	-0.887	0.375
Creatinine (mg/dL)	1.2±0.92	0.91±0.92	1.9	0.057
eGFR (mL/min/1.73 m^2)	99.06±57.2	102±57.87	-0.37	0.71
HbA1c % (mmol/mol)	9.65±2.59	10.37±2.50	-1.5	0.13

[Table/Fig-3]: Biochemical and haematological variables in patients with T2DM according to the presence or absence of anaemia.
Z-test was applied and statistical significance was set at p-value less than 0.05

DISCUSSION

The results of the present study estimated the prevalence of anaemia to be 47.7% (male) and 52.3% (female) in individuals with T2DM. Overall, a remarkable incidence of anaemia (57.3%) was observed which was relatively higher compared to 49% in the general non diabetic population reported in the same region and another study from southern India which showed 12.3% prevalence of anaemia among diabetic patients [6,15]. Among the anaemics, majority (52.4%) were found to have normocytic anaemia.

Scanty information exists on the prevalence and factors of anaemia amongst people with diabetes in India. A study by Little M et al., among the rural population, showed a higher risk of anaemia among women but the prevalence was found to increase with age among men [15]. Pathak J et al., observed the risk of anaemia in diabetic individuals to be 2.04 times higher than non diabetics, with low EPO levels as the most common cause [16].

The prevalence of anaemia in the study by Little M et al. was 39.3% among men and 57.2% among women (p<0.001) [15], compared to 47.7% in diabetic men and 52.3% in diabetic women in this study. The higher incidence of anaemia in this study may be due to the limited sample, with poorly controlled diabetes, who may be susceptible to impaired EPO production and its release due to diabetic nephropathy [24,25]. The study indicated no significant difference in the risk of anaemia between males and females. This finding is consistent with the previous study [26].

Previous researches among the Caribbean population [27], Ethiopians [28], and Caucasians [2,29], have suggested that patients with diabetes have an increased risk of anaemia when compared with non diabetic subjects. It was comparable or lower than the findings of this study, due to the variation in the sociocultural aspect and the geographical location along with varying age of the study population.

It has been speculated that the risk for anaemia may be aggravated in poorly controlled diabetes than in controlled settings [30]. However, the parameters for diagnosing diabetes (HbA1c and FBS) had no significant association with anaemia in this study. Against the expected results, higher blood glucose levels were observed in non anaemic subjects, similar to another study [31].

Previous studies on diabetic patients with normal renal functions showed that longstanding poorly controlled diabetes is associated with normocytic normochromic anaemia [24,32]. The high prevalence of normocytic and microcytosis in this study suggests the importance of non renal causes of anaemia in diabetic patients, having implications on the diagnostic and therapeutic options. A statistically significant difference was observed among the elderly population on the comparison between anaemics and non anaemics. This was in concordance with prior reports, since age was associated with low haemoglobin levels among the general population irrespective of their health status [25,33]. Hence, there is a need for close monitoring and adequate care for elderly patients with diabetes, who are highly vulnerable to anaemia and its cardiovascular complications.

Various community based demographic studies among the middle aged population have proved a significant association of the combination of nephropathy and anaemia as an independent risk factor for stroke and cardiovascular events [12-14]. Hence, correction of anaemia in such high risk populations with diabetes might be of favourable benefit [34]. However, such measures must be carefully balanced against the financial burden of treatment in low resource settings.

Limitation(s)

The observed findings may overestimate the real burden of anaemia among diabetic patients, as the study was conducted in a tertiary care hospital. Since, this study did not probe into the causes of anaemia, there is a need for further research among this targeted population. The role of EPO, reticulocyte count, iron studies, markers of chronic inflammation, and the incidence of haemoglobinopathies were not studied. Other modifiable factors such as helminthic infections, malaria, HIV, and non modifiable factors such as parity, menstruation, and pregnancy, which have the significant potential for causation, were not accounted for, in this study.

CONCLUSION(S)

Patients with T2DM have an independent risk for anaemia irrespective of renal insufficiency, posing a significant adverse effect on the quality of life and the progression of the underlying disease with high cardiovascular morbidity and mortality. This study findings strengthen the facts that the development of anaemia may predate the occurrence of renal insufficiency. With awareness and correction of anaemia bearing a significant role in the prevention of cardiovascular complications, it is thus highly recommended that management of diabetic patients should have mandatory routine haematological tests, with consideration of advancing age, and poor glycaemia control, and therefore in developing interventions to optimise clinical outcomes.

Further studies on the causation and role of correction of anaemia in patients with diabetics and its effect on cardiovascular complications, will be of utmost interest.

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