Anemia in Male with Type 2 Diabetes Mellitus

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Abstract

Diabetes mellitus (DM) is the leading cause of many chronic diseases. Anemias in men with diabetes mellitus greatly contribute to the pathogenesis and progression of cardiovascular disease and aggravate diabetic nephropathy and retinopathy. The present study was carried out to estimate the Hb level, to determine the total count of RBC and reticulocyte count to evaluate the anemia and FBG & HbA_1c to assess their glycemic status. The cross-sectional study was conducted in the Department of Physiology, Dhaka Medical College, Dhaka from January, 2011 to December, 2011. Total 90 male subjects were selected with the age ranging from 40 to 60 years. Among them 60 subjects were diabetic, 30 subjects were with controlled (B_1) and other 30 subjects with uncontrolled (B_2) type 2 diabetes mellitus. They were selected from Outpatient Department of BIRDEM Hospital by random basis. And the rest 30 age-matched, healthy non-diabetic male subjects were considered as control group (A) for comparison. They were selected from Dhaka City through personal contact. For statistical analysis unpaired Student's t-test was performed. The result was expressed as mean (±SD) among the groups. In this study, there are significant decrease in Hb level, total RBC count and increase

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in reticulocyte count in study groups. The prevalence of anemia is high in patients with type 2 DM, which affects quality of life of diabetic patients and is associated with disease progression and co-morbidities that contribute significantly to the increasing risk of cardiovascular diseases.

Key words: Type 2 diabetes mellitus, HbA_1c, Hb. level. RBC count, reticulocyte count.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder which has a great impact worldwide. Diabetes mellitus is characterized by an elevation of blood glucose level caused by a relative or absolute deficiency of insulin. Type-2 DM may cause insulin resistance which can lead glucose accumulation in the circulation and consequently a hyperglycemic state, generating homeostatic and systemic imbalance.[3]

Studies from 91 countries it is found that in 2010 there will be 285 million people worldwide with diabetes, with considerable disparity between populations and regions. It is also found that the pattern of diabetes varies considerably according to countries' economic status. For developed countries, the majority with diabetes are aged over 60 years, whereas for developing countries most people with diabetes are of working age, between 40 and 60 years. This difference is likely to still be present in 2030. Population growth, ageing of populations and urbanization with associated lifestyle change is likely to lead to a 54% increase in worldwide numbers with diabetes by 2030.[1]

Epidemiological data showed that in 2012 there were 371 million people affected with the disease in the world, and it is estimated that in the year of 2030 we will have about 552 million diabetics. This worldwide prevalence affects about 7% of the general population[2]. In Bangladesh prevalence of diabetes was found 9.2% in the year of 2013.[18]

According to International Diabetes Federation (IDF) Diabetes Atlas Seventh Edition, it is estimated that about 415 million adults aged 20-70 living with diabetes and 5.0 million deaths were attributed to diabetes globally in 2015.[19] According to WHO, diagnostic criteria of diabetes

mellitus are fasting blood glucose≥ 7.0 mmol/l, 2 hrs after blood glucose ≥ 11.1mmol/l and $HbA1_C$ ≥6.5%.[14]

DM is a common disease, caused by many etiological factors and oxidative damage is one of the risk factors to play a major role in the pathogenesis of this disease.[4] High glucose level in diabetes inhibits G6PD expression and activity in endothelial cells, kidney, liver and RBCs, which leads to oxidative damage, cellular dysfunction and organ damage. This oxidative damage causes early destruction of RBCs which leads to anemia.[5] High glucose concentrations increase the level of Reactive Oxygen Species (ROS). The ROS, generated by hyperglycemia, causes many of the complications of diabetes, such as nephropathy, retinopathy, and neuropathy. Recent evidence indicated that oxidative damage markedly rose in type- 2 diabetes mellitus.[6]

Hyperglycemia has a direct relationship with the development of an inflammatory condition showed by the increased expression of pro-inflammatory cytokines. The elevation of pro-inflammatory cytokines plays an essential role in insulin resistance and induces the appearance of cardiovascular complications diabetic micro and macro vascular disease, kidney disease and anemia.[12, 21]

According to Escorcio et al. by increasing pro- inflammatory cytokines, anti-erythropoietic effect occurs, also promotes apoptosis of immature erythrocytes causing a decrease in the number of circulating erythrocytes and consequently causing a reduction of circulating hemoglobin.[22] Anemia represents an emerging global health problem that negatively impacts quality of life.[23] The anemic framework promotes reduced exercise capacity, fatigue, anorexia, depression, cognitive dysfunction, decreased libido, and other factors, which increase cardiac risk patients and depress the quality and life expectancy of the same.[24]

Some observer conducted a study to find out the association between anemias with new onset diabetes. They found that out of 1500 patients, 83 (5.5%) were anemic and 45 of the 83 patients were found to have identifiable cause of anemia.[7] Again, some people (Meir (2003)) also observed the signs of hemolysis in diabetic subjects and they found decreased hemoglobin concentration, and increased reticulocyte count in them.[8] Some researchers (Ranil et al. (2010)) observed that the prevalence of anemia among the type 2 diabetes subjects was 12.3%. Similar study was made by Craig et al. (2005). They found that 8 of the 45 male diabetic patients (17.8%) were classified as anemic.[9; 10] A cross-sectional study was made by Thomas et al. (2003) on 820 patients with diabetes mellitus. Among them, about 190 patients (23%) had anemia of unrecognized origin.[11]

Under these circumstances, anemia in patients with diabetes must be treated once diagnosed, since it may contribute to the pathogenesis and progression of cardiovascular disease and serious diabetic nephropathy and retinopathy. Anemia in diabetic person has a significant adverse effect on quality of life and is associated with disease progression and the development of co-morbidities. The regular screening for anemia, along with other complications associated with diabetes, can help slowing the progression of vascular complications in those patients.[12, 13]

MATERIALS AND METHODS

This cross sectional study was done in the department of Physiology in Dhaka Medical College Dhaka from January, 2011 to December 2011.Protocol of this study was approved by Ethical review committee of Dhaka Medical College and Diabetic Association of Bangladesh. For this study 60 male, age (40-60 years), diabetic subjects with FBG level ≥7.0 mmol/l and HbA_1c ≥ 6.5 % and duration of diabetes > 3 years were selected from BIRDEM hospital. All the study subjects were on oral hypoglycemic drugs. Thirty healthy adult male were considered as control group for comparison. After selection of the subjects, the nature, purpose and benefit of the study were explained to each subject in details and were encouraged for voluntary participation. They were also allowed to withdraw from the study whenever they feel like. Informed written consent was taken from the participants. Before taking blood, detailed family and medical history were taken. Anthropometric measurement of the subjects was done and blood pressure was measured. All the information's were recorded in a prefixed questionnaire. With aseptic precaution, 5 ml of venous blood was collected from ante-cubital vein by a disposable plastic syringe from each subject for estimation of $HbA_{1c,}$ andFBG level was estimated in the laboratory of the Biochemistry Department of BIRDEM hospital and the G6PD tests were done in the laboratory of the Department of chemical biochemistry, AFIP, Dhaka Cantonment, Dhaka. All the parameters were expressed as mean ± SD (standard deviation). For statistical analysis was done by unpaired Student's t- test. P value < 0.05 was accepted as level of significance. Statistical analyses were performed by using a computer based statistical program SPSS (Statistical package for social science) Version 12.

RESULTS

A total number of 90 adult male subjects were selected for this study. Among them, 60 subjects were adult male with type 2 diabetes and 30 healthy subjects with same age range were selected as control group for comparison. The mean (±SD) FBG levels were 5.12 ±0.76, 7.48 ±1.27 and 9.14 ±2.10 mmol/L respectively in control subjects(group A), Controlled diabetes mellitus (group B_1)and Uncontrolled diabetes mellitus (group B_2). In this study, the mean (±SD) FBG level was significantly (p<0.0001) higher in group B_1 and group B_2 in comparison to that of group A. Again, FBG level was significantly (p<0.0001) higher in group B_2 than that of group B_1. The mean (±SD) HbA_{1c} levels were 5.83±0.75, and 9.98 ±2.10 in group B_1 and B_2 respectively. In this study, the mean (± SD) HbA_{1c} level was significantly (p<0.0001) higher in group B_2 than that of group B_1. (Table-I)

Table I. FBG level in different groups (n=90) and HbA_1c level in study groups (n=60)

Parameters	Group A (n=30)	Group B_1 (n=30)	Group B_2 (n=30)
FBG (mmol/L)	5.12±0.76 (3.80-6.90)	7.48±1.27 (5.10 -9.90)	9.14±2.10 (6.00 -15.50)
HbA_{1c} (%)		5.83 ±0.75 (4.30-6.90)	9.98 ±2.10 (7.30-15.10)
Statistical analysis			
Groups	FBG (mmol/L) (p value)		HbA_{1c} (%) (p value)
A vs B1	0.0001***		
A vs B2	0.0001***		
B1 vs B2	0.0001***		0.0001***

Results are expressed as Mean ±SD & figures in parenthesis indicate the range.

The test of significance was calculated and p values <0.05 was accepted as level of significance.

Group A   : non- diabetes   ns = Not significant
Group B_1 : Controlled diabetes   * = Significant at P<0.05
Group B_2 : Uncontrolled diabetes
n   = Number of subjects   ** = Significant at P<0.01
***   = Significant at P<0.001

The mean (±SD) hemoglobin levels were 14.24 ±0.75, 12.88±1.16 and 11.72±1.42 gm/dl in control non-diabetic (group A), Controlled diabetes mellitus (group B_1) and Uncontrolled diabetes mellitus (group B_2) respectively. In this study, the mean hemoglobin level was significantly (p <0.0001) lower in group B_1 and group B_2 in comparison to that of group A. Again, this value was significantly (p <0.001) lower in group B_2 than that of group B_1. The mean (±SD) RBC count were 5.09 ±0.50, 4.86 ±0.55 and 4.58 ±0.77 10^{12}/L in groups A, B_1 and B_2 respectively. In this study, the mean RBC count was lower in group B_1 and group B_2 than that of group A. The mean RBC count in group B_2 was lower than that of group B_1. In comparison to group A, it was significantly (p<0.003) lower in B_2 but non-significant in B_1. The mean (± SD) reticulocyte count were 1.02 ±0.53, 1.49 ±0.93 and 2.26 ±0.99 % in group A, B_1 and B_2 respectively. In this study, the mean reticulocyte counts in different groups were within normal range. But the differences of these mean values were significantly lower in group B_2 (p <0.0001) and in group B_1 (p <0.019) than group A. Within the study group reticulocyte count was significantly (p <0.003) higher in group B_2 than that of group B_1. (Table- II).

Table II: Hemoglobin conc., total count of RBC, Reticulocyte count in different groups (n=90)

| Parameters	Group A (n=30)	Group B1 (n=30)	Group B2 (n=30)
Hb level (gm/dl)	14.24 ±0.75 (13.00-15.90)	12.88 ±1.16 (10.20-15.30)	11.72 ±1.42 (8.80-15.00)
RBC count (1012/L)	5.09 ±0.50 (4.35-6.96)	4.86 ±0.55 (3.99-6.47)	4.58 ±0.77 (3.04-6.53)
Reticulocyte count (%)	1.02 ±0.53 (1.50-3.00)	1.49 ±0.93 (0.20-4.00)	2.26 ±0.99 (0.50-4.00)

Statistical analysis

Groups	Hemoglobin (p value)	RBC count (p value)	Reticulocyte count (p value)
A vs B1	0.0001***	0.097ns	0.019*
A vs B2	0.0001***	0.003**	0.0001***
B1 vs B2	0.001**	0.108ns	0.003**

Results are expressed as Mean ±SD & figures in parenthesis indicate the range.
The test of significance was calculated and p values <0.05 was accepted as level of significance.
Group A   : non- diabetes   ns = Not significant
Group B1 : Controlled diabetes   *   = Significant at P<0.05
Group B2 : Uncontrolled diabetes n   = Number of subjects
**   = Significant at P<0.01*** = Significant at P<0.001

In this study, group B_1 (n=30), mean Hb level <13gm/dl was found in 15 (50.0 %) subjects and ≥13gm/dl was found in 15 (50.0 %) subjects. And group B_2 (n=30), mean Hb conc. <13gm/dl was found in 26 (86.7 %) subject and ≥13gm/dl was found in 4 (13.3 %) subjects. (Figure-I & II).
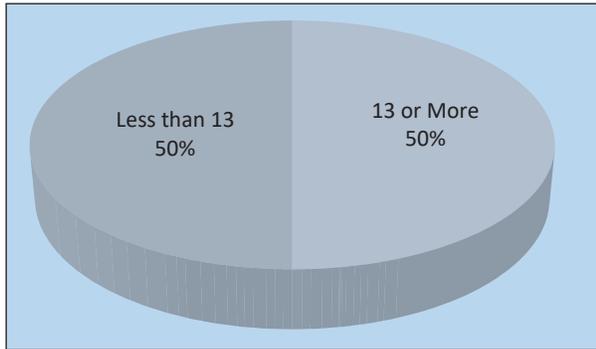
Figure 1. Distribution of study subjects (group B1 as controlled diabetes) by Hb level (n=30)
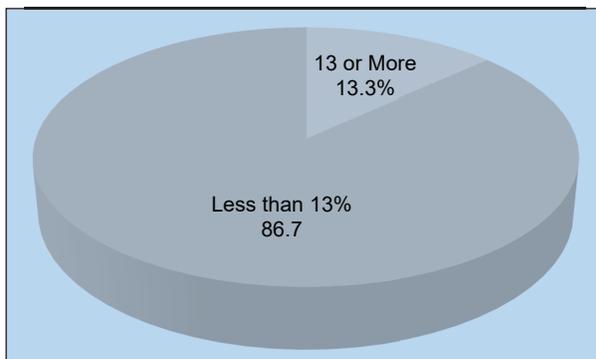
Figure 2. Distribution of study subjects (group B2 as uncontrolled diabetes) by Hb level (n=30)

DISCUSSION

The present study was undertaken to observe anemic status in type 2 diabetic male subjects. For this, fasting blood glucose (FBG) level and HbA_1c level were done to observe their glycemic status, and hemoglobin level, total count of RBC and reticulocyte count were also studied in all these subjects to find out their hemolytic status. Furthermore, FBG level, Hb conc., total count of RBC and reticulocyte count were also studied in apparently healthy persons to find out the base line data and also for comparison.

Hb conc. was significantly lower in diabetic males than that of the non-diabetic males. Similar findings were made some authors.[7] In our country, Akhter et. al.[14] showed Hb conc. was significantly lower in diabetic females than that of the non-diabetic females.

Chronic disease such as DM, are accompanied by mild to moderate anemia, often called anemia of chronic disease.[15] There are decreased values of Hb, hematocrit and red blood cells, which can be associated with a normocytic normochromic anemia, just like of an anemia of chronic disease. In mild to moderate anemia survival of red blood cells are decreases; it is about 80 days instead of 120 days. This phenomenon is attributed to hyperactivity state mononuclear phagocyte system, triggered by infectious, inflammatory, or neoplastic process, leading to early removal of circulating red blood cells.[16]

In the present study, early hemolysis is also observed in this study by decreased Hb%, RBC count and increased reticulocyte count. The reticulocytosis may be due to compensatory response to hemolysis. And HbA_1c test was done to assess their glycemic control, as HbA_1c express the average amount of glucose in the last three month.

CONCLUSIONS

In this study, there are significant decrease in Hb conc., total count of RBC and increase in reticulocyte count in study groups. Nevertheless mean value of RBC and reticulocyte count were within normal range, but Hb conc. was below the normal limit. The prevalence of anemia is high in patients with type 2 DM. This set of changes characterizes the anemia as chronic disease, which has a significant adverse effect on quality of life of diabetic patients and this is associated with the progression of the disease; the development of co-morbidities significantly contributes to the increased risk of cardiovascular disease.

REFERENCES

1. Shaw JE, Sicree RA, &Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes research and clinical practice, 2010; vol.87, no.1, pp.4-14.

2. Pereira PF, Alfenas RDCG, & Araujo RMA, 'Does breastfeeding influence the risk of developing diabetes mellitus in children? A review of current evidence,' Journal de Pediatria, 2014; vol.90, no.1, pp.7-15.

3. Zhang X, cui X, Li F, et al. Association between diabetes mellitus with metabolic syndrome and diabetic microangiopathy. Experimental and therapeutic medicine. 2014; vol.8, no.6, pp.1867-1873.

4. Wan GH, Tsai C, &Chiu DTY. Decreased blood activity at glucose-6-phosphate dehydrogenase, associates with increased risk for diabetes mellitus. Endocrine, 2002; vol. 19, pp. 191-195.

5. Zhang Z, Liew CW, Handy DE, Zhang Y, Leopold JA, Hu J, Guo L, Kulkarni RN, Loscalzo J &Stanton RC. High glucose inhibits glucose-6-phosphate dehydrogenase, leading to increased oxidative stress and â-cell apoptosis. The FASIB Journal, 2010; vol. 24, no.5, pp. 1497-1505.

6. West CI. Radicals and oxidative stress in diabetes. British Diabetic Association, 2000; vol.17, pp. 171-180.

7. Pilona AP, Litonjua P, Devaraj S, Santa LA &Raskin, P. Anemia associated with new-onset diabetes: improvement with blood glucose control. Endocrine practice, 2002; vol. 8, no. 4, pp. 276-281.

8. Meir A, Kleinman Y, Rund D &Da'as N 2003. Metforming induced hemolytic anemia in a patient with glucose-6- phosphatedehydrogenase deficiency. Diabetes care, 2002; vol. 26, no.3, pp. 956-57.

9. Ranil PK, Raman R, Rachepalli SR, Pal SS, Kulothungan V, Lakshmipathy P, Satagopan U, Kumaramanickavel G & Sharma T. Anemia and diabetic retinopathy in type 2 diabetes mellitus. J Assoc Physicians India, 2010; vol.58, pp. 91-4.

10. Craig KJ, Williams JD, Riley SG, Smith H, Owens DR, Worthing D, Cavill I & Phillips AO. Anemia and diabetes in the absence of nephropathy. Diabetes Care, 2005; vol. 28, no.5, pp. 1118-23.

11. Thomas MC, MacIsaac RJ, Tsalamandris C, Power D, Jerums G. Unrecognized anemia in patients-with diabetes: a cross-sectional survey. Diabetes Care, 2003; vol.26, no. 4, pp.1164-9.

12. Angelouse A, & Larger E. Anaemia, a common but often unrecognized risk in diabetic patients: a review. Diabetes & metabolism, 2005; vol.41, no.1, pp.18-27.

13. Singh DK, Winocour P & Farrington K. Erythropoitic stress and anemia in diabetes mellitus. Nature reviews endrocrinology, 2009; vol.5, no.4, pp. 204-210.

14. WHO. Anemia. 2012; World health organization.

15. Akhter N, Begum N, Ferdousi S. Glucose 6-phosphete dehydrogenase (G6PD) status in female type 2 diabetes mellitus and its relationship with HbA1C. J Bangladesh Soc Physiol, 2010; Dec; 5(2): 60-65.

16. Andrews M, & Arredondo M. Ferritin levels and hepcidin mRNA expression in peripheral mononuclear cells from anemic type 2 diabetic patients. Biological trace Element Research, 2012; vol. 149, no.1, pp. 1-4.

17. Barbieri J, Fontela PC, Winkelmann ER, Zimmermann CEP, Sandri YP, Mallet EKV, &Frizzo MN. Anemia in patients with type 2 Diabetes Mellitus. 2015; vol.2015,.available from http://dx.doi.org/10.1155/2015/354737

18. Rahman MS, Akter S, Abe SK, Islam MR, Mondal NMI, Rahman JAMS, RahmanMM. Awareness, Treatment, and Control of Diabetes in Bangladesh: A Nationwide Population-Based study. PLoS one 2015; 10(2): e0118365.

19. IDF Diabetes Atlas Seventh Edition. Available at: http://www.diabetesatlas.org/key-messages.html.(acc essed:1st April 2016).

20. Pérez B M, Díez IDLT, and Coronado ML. Mobile health applications for the most prevalent conditions by the World Health Organization: review and analysis. Journal of Medical Internet Research, 2013; vol. 15, no. 6, article e120.

21. Fava S, Azzopardi J, Ellard S, and Hattersley A. T. ACE gene polymorphism as a prognostic indicator in patients with type 2 diabetes and established renal disease. Diabetes Care, 2001; vol. 24, no. 12, pp. 2115–2120.

22. Escorcio CSM, Silva HF, Junior GBS, Monteiro MP, and Gonçalves RP. Evaluation of anemia treatment with EPO and oral and iv iron in patients with chronic kidney disease under hemodialysis. RBSA, 2010; vol. 42, no. 2, pp. 87–90.

23. MacCiò A and Madeddu C. Management of anemia of inflammation in the elderly. Anemia 2012; vol. 2012, Article ID 563251, 20 p.