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Risk of anaemia in Type 2 diabetes patients in the absence of renal impairment

KEYWORDS: Anaemia, Type-2 Diabetes Mellitus, HbA1c

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ABSTRACT

Introduction: Anaemia is one of the world's most common preventable conditions, yet it is often overlooked. Aim: To determine the incidence of anaemia in type 2 diabetes patients with normal renal function and assess the association of other factors related to diabetes with the risk of anaemia. Methods: The study group comprised 600 patients with type-2 diabetes. Patients were divided into groups according to glycemic control, gender and age. Results: 40% of the patients had anaemia. The odds of developing anaemia was higher in patients with poorly controlled diabetes (HbA1c > 7.5%) compared to those with controlled diabetes (≤7.5%) and in patients of age ≥ 60 years compared to those of age < 60 years ($p < 0.05$). The odds of anaemia was similar in males and females ($p = 0.26$). Conclusion: This study indicated that poor glycemic control and old age are associated with the incidence of anaemia. Our findings suggest that treatment criteria for diabetes should include routine haematological tests.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder of great impact worldwide. Its worldwide prevalence is increasing fast among developing countries. The type 2 diabetes affects about 7% of the population[1].

Glycated Haemoglobin A1c (HbA1c) has been adopted by physicians as a convenient way to screen for diabetes and to monitor therapy. HbA1c is the most predominant fraction of HbA1 and it is formed from the glycation of the terminal valine unit of the β chain of Haemoglobin. HbA1c should be below 7% in all diabetic patients according to the American Diabetes Association, so as to prevent the development of micro vascular complications[2]. Apart from being affected by the blood glucose levels, HbA1c is also affected by pregnancy[3,4], uremia[5], hemolytic anaemia[6], hemoglobinopathies[7], acute and chronic blood loss[8,9], Vitamin B12 and folate deficiencies. Iron deficiency anaemia is also shown to have a considerable effect on HbA1c levels[10]. It may not be accurate surrogate to ascertain glycemic control in certain conditions that affect the concentration, structure and functions of hemoglobin [2,3].

Anaemia is the most common blood disorder and a common finding in patients with diabetes [1,2]. 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 anaemia in diabetic patients is mostly associated with the presence of renal insufficiency. Thus, patients with diabetes have a greater degree of anaemia for their level of renal impairment than non-diabetic patients presenting with other causes of renal failure [11-15].

Diabetes does not directly cause anaemia, but certain complications and conditions associated with diabetes can contribute to it. Both diabetes-related kidney disease (nephropathy) and nerve damage (neuropathy) can contribute to the development of anaemia. Severe symptomatic autonomic neuropathy causes efferent sympathetic denervation of the kidney, loss of appropriate erythropoietin, damage to the renal interstitium, systemic inflammation and inhibition of erythropoietin release [11-15]. Both chronically high blood glucose levels and high blood pressure can cause kidney damage.

Many people who have diabetes have nutritional deficiencies that can cause anaemia. Nutrient deficiencies can be caused by either not eating enough nutrients or by the body's inability to absorb the nutrients that are eaten. Deficiencies in iron, vitamin B12 and folate all can cause anaemia [16,17]. Oral hypoglycemic agents like Metformin which is most widely prescribed treatment for people with type 2 diabetes. Long term use of this drug can cause malabsorption of vitamin B12 leading to anaemia [18,19].

There are many reports on the presence of anaemia in diabetic patients with renal insufficiency, but limited study [16,20] exists on the incidence of anaemia in diabetics prior to the evidence of renal impairment. This may explain why most diabetic patients with normal renal function are rarely tested for anaemia. The need for more studies on incidence of anaemia in diabetic patients prior to renal impairment has therefore become imperative, in order to increase the level of awareness and understanding of anaemia amongst diabetic patients.

In the present study therefore, we aimed at demonstrating the incidence and risk of anaemia in type 2 diabetic patients with normal renal function. In addition, the incidence and risk of anaemia in these patients were assessed according to gender, age and glycemic control.

MATERIALS and METHODS

Subjects:

This cross sectional study comprised 600 type-2 diabetic patients with normal renal functions. We used the electronic data of patients of Chennai medical college hospital and research centre, Irungalur, Trichy, TN., who consulted during April 2016 to December 2016. The study participants were residents of in and around Trichy, Tamil Nadu, South India.

Only electronic records (clinical and laboratory) of initial visit to the hospital were extracted for the purpose of this study. Laboratory data included Serum creatinine, haematocrit, haemoglobin concentration, blood glucose and glycated haemoglobin (HbA1c). The presence of anaemia was defined by a haemoglobin level < 13.0 g/dL in men and < 12.0 g/dL in women. Normal renal function (i.e., absence of renal impairment) was defined as serum creatinine level < 1.5 mg/dL. Other information obtained electronically were socio demographic

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factors (gender, age, ethnicity, smoking status and duration of T2DM) and clinical findings on first visit [blood pressure (BP), medications, eGFR and diabetic complications. The diabetic patients were divided into groups according to: 1) Glycemic control [patients with controlled diabetes (n = 357) and those with poorly controlled diabetes (n = 243)]; 2) Gender (males, n = 281; females, n = 319); 3) Age (<60 years, n = 452; ≥60 years, n = 148). The controlled diabetic group comprised those whose glycated haemoglobin concentration (HbA1c) was ≤7.5%. The poorly controlled diabetic comprised those whose HbA1c level was >7.5%. Group designation, patients demographics and clinical features are listed in Table 1.

To be included in the study, all patients had to 30 years of age or older and without renal insufficiency (serum creatinine level of <1.5 mg/dL). 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 haemolytic / iron deficiency anaemia or genetic differences in the haemoglobin molecule (haemoglobinopathy) such as sickle-cell disease and other systemic disorders that could result in anaemia and pregnancy. The presence of anaemia was defined by a haemoglobin level < 13.0 g/dL in men and <12.0 g/dL in women based on definition of World Health Organization (WHO) [17]. Serum creatinine, Fasting blood glucose and HbA1C were estimated using Mindray BS-420 chemistry analyser.

Statistical Analysis

Descriptive data are presented as means and standard deviations (SD). Data analysis between two groups was compared using two-tailed independent sample t-test. Two-tailed Pearson's partial correlation coefficient was used to determine age-adjusted correlations between variables. Logistic regression analysis was used for the analysis of associations between anaemia and independent variables. Data were analysed using IBM SPSS statistics 20. $p < 0.05$ was considered as significant.

RESULTS

Demographic and clinical characteristics of patients are as shown in Table 1. Mean haemoglobin values were significantly higher in persons with controlled diabetes compared to persons with poorly controlled diabetes ($p < 0.001$) and in patients of age < 60 years compared to those who are ≥60 years ($p < 0.05$). Significantly higher haematocrit was noted in diabetic males and in patients with controlled diabetes compared to females and those with poorly controlled diabetes ($p < 0.001$ and $p < 0.05$) respectively. On the other hand, mean haemoglobin indicated no gender differences and haematocrit indicated no age differences.

Table 1: Demographic and clinical characteristics of patients

All Diabetics (n = 600)	Poorly Controlled Diabetes (n = 243) vs. Controlled Diabetes (n = 357)	Diabetic Males (n=281) vs. Diabetic Females (n = 319)	Diabetics≥60yrs(n=148) vs. Diabetics < 60 years (n = 452)	
Age (years)	48.8 ± 14.2	48.7 ± 13.6 vs. 49.2 ± 12.3	48.9 ± 14vs. 48.3 ± 13.6	59.5 ± 2.8 vs. 48.2 ± 9.6
HbA1c (%)	11.7 ± 5.77	15.6 ± 7.1*** vs. 6.5 ± 0.9	10.2 ± 4.65 vs. 13.0 ± 6.35*	13.4 ± 7.01 vs. 11.3 ± 5.40
FBG (mg/dL)	167.6 ± 48.18	185.7 ± 53*** vs. 145.0 ± 28	160.8 ± 36.27 vs. 173.7 ± 55.65	175.5 ± 65.6 vs. 166 ± 43.2
S.Cr (mg/dL)	0.95 ± 0.29	1.02 ± 0.27* vs. 0.87 ± 0.28	0.93 ± 0.28 vs. 0.97 ± 0.29	1.0 ± 0.24 vs. 0.9 ± 0.30
Hb (g/dL)	13.1 ± 1.02	12.7 ± 0.75 vs. 13.7 ± 1.09***	13.4 ± 0.91 vs. 12.9 ± 1.07	12.4 ± 0.82 vs. 13.2 ± 1.15*
HCT (%)	39.6 ± 3.09	38.6 ± 2.88 vs. 40.9 ± 2.82***	40.4 ± 3.01* vs. 38.9 ± 2.98	39.0 ± 4.21 vs. 39.4 ± 3.22

Abbreviations: HbA1c = Glycated hemoglobin concentration; FBG = Fasting blood glucose; S. Cr = Serum creatinine; Hb = Hemoglobin; HCT = Hemotocrit. *p < 0.05; **p < 0.01; ***p < 0.001. Data = mean ± standard deviation.

Two hundred forty (240) of the 600 diabetic patients presented with anaemia representing 40% of incidence of anaemia **(Figure 1)**. 25% (n =60) of the patients with poorly controlled diabetes; 0.6% (n = 2) of those with controlled diabetes; 19% (n = 53) of the diabetic men; 10.5% (n = 33) of the diabetic women; 35.7% (n = 52) of the older patients of age ≥ 60 years and 10.3% (n = 46) of patients of age < 60 years, were anaemic.

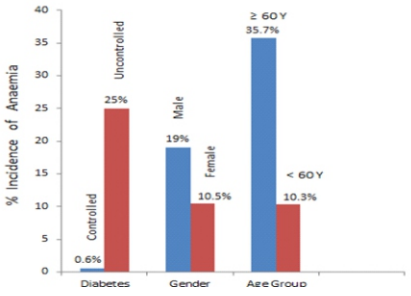

Fig. 1. The % incidence of anaemia Vs diabetic patients (According to glycemic control, gender and age)

DISCUSSION

In the present cross-sectional study, patients had high incidence of anaemia (40%). Interestingly, the parameters HbA1c and FBG had significant, negative correlations with the indicator variables of anaemia. A previous studies reported that 7.2% of diabetics with normal renal function had anaemia [14,15,16] . HbA1c is majorly affected by the blood glucose levels alone. However, certain studies have proven that the HbA1c levels are altered by various other coexisting factors, along with diabetes, especially anaemia, which is a major public health problem in developing countries like India.

The higher incidence of anaemia observed in our study in those who were poorly controlled diabetes, who may be susceptible to impaired erythropoietin production and release. Lim SK [20] reported that the levels of erythropoietin are associated with diabetes, and he also reported that, high glucose stimulates erythropoietin production and erythropoietin receptor phosphorylation in rat glomerular epithelial cells. Thomas et-al reported [21], even in the absence of renal impairment, 71% of diabetic anaemic patients had functional erythropoietin deficiency, although most had other evidence of nephropathy.

It is not known whether the incidence of anaemia in diabetic patients is dependent on haematological effects of other risk factors related to diabetes mellitus. We therefore evaluated the risk of anaemia in the diabetic cohorts with regard to age, sex and glycemic control of the patients. The mechanisms behind the greater risk of anaemia in poorly controlled diabetes than in controlled diabetes are not very clear. However, it has been. Other factors which have been reported to increase the risk of anaemia include; systemic inflammation [12]; damage to renal architecture produced by chronic hyperglycemia and consequent formation of advanced glycation end products [1,2,13]; and depressed androgen levels induced by diabetes [14]. It is speculated that these conditions may be aggravated in poorly controlled diabetes than in controlled diabetes. Our finding therefore suggest that a reduction of blood glucose levels and the targeting of acceptable glycated haemoglobin levels would help reduce the risk of anaemia in the diabetic population.

Our data also indicated greater odds of anaemia in patients of age ≥ 60 years when compared to those of age < 60 yrs. This result was expected since age is associated with both haemoglobin levels and anaemia irrespective of health status [22,23]. Increased odds of

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anaemia has also been found in previous studies [5,22,23] among older diabetic patients and consistent with the present findings. These findings indicate the need for proper diabetic care and management for diabetic senior citizens, who have limited food choices and are more vulnerable to iron- deficiency anaemia. Furthermore, our data indicated no significant difference in the risk of anaemia between males and females. This finding is consistent with a previous study [23]. However, in another study involving patients with moderate levels of renal deficiencies, gender difference in the risk of anaemia has been reported [5].

In conclusion, a high incidence of anaemia was observed in diabetics without renal insufficiency. Our data also suggested that poor glycemic control and old age are associated with the incidence of anaemia in diabetic patients with normal renal function. Correction of anaemia may have a significant role in prevention of other diabetic complications, thus we recommend that treatment criteria for diabetes should include routine hematological tests and take into consideration the inevitable consequences of aging and poor glycemic control, in order to make optimal therapeutic decisions for the treatment of diabetes mellitus in adults.

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