

Original Research Article

Prevalence of anaemia in patients with type 2 diabetes mellitus at a tertiary care centre in Sri Lanka

Abstract

Anaemia encountered frequently with Type-2 Diabetes Mellitus(T2DM) leads to development of micro and macro-vascular complications. Although many studies describe prevalence of anemia among diabetics in other countries no studies are available for Sri Lanka. The aim was to determine prevalence and causes of anaemia among patients with T2DM attending the Family Practice Centre, University of Sri Jayewardenepura and describe relationship between anaemia and associated factors.

Full Blood Counts, S, Ferritin were performed and T2DM patients with haemoglobin<12g/dl (females) and <13g/dl (males) were identified, red cell indices analysed. Mean haemoglobin was 11.98±1.79 g/dl (12.92±2.49 g/dl in males, 11.60 ± 1.24 g/dl in females). 35.29% (36/102) of patients were anaemic with female preponderance. Iron deficiency anaemia was present in 11.11 % (4/36), heemoglobinopathy in 11.11% (4/36) and anaemia of chronic disorder in 77.78% (28/36)

Anaemia significantly related to age (p=0.036), gender(p=0.01),duration of diabetes mellitus(p=0.002) and presence of Chronic-Kidney-Disease(p=0.001).Retinopathy(p=0.05) and treatment modality had no association with prevalence of anaemia(p=0.322).

Prevalence of anaemia among T2DM patients in Sri Lanka is high specially with increasing age , female gender , duration of disease and corresponds to regional countries.. As treatment

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Comment [VP4]: S. Ferritin

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Comment [VP6]: cannot be considered as Hb has gender variation

Comment [VP7]: other reasons to be ruled out in females

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of anaemia of chronic disorder is treatment of underlying disease management of diabetes will reduce prevalence of anaemia.

Key Words

Anemia in Type 2 Diabetes mellitus, associations of anemia in Type 2 Diabetes mellitus, Causes for anemia in diabetics

Introduction

Diabetes Mellitus is a chronic metabolic disease characterized by hyperglycemia caused by insufficient insulin secretion or diminished insulin action or both. It is associated with the risk of micro vascular complications (diabetic retinopathy, neuropathy and nephropathy) and this risk increases with the duration of the disease.¹ Types of Diabetes Mellitus include Type 1, Type 2 and Gestational Diabetes Mellitus.

Type 2/Non- Insulin dependent Diabetes/Adult-onset diabetes is the most common type of DM and occurs due to two primary pathogenic mechanisms. Lack of insulin secretion and reduction of sensitivity in skeletal muscles cells and liver cells to insulin.²

Comment [VP10]: Sentence repeated in 1st para

According to Global report on diabetes, WHO, Geneva, 2016 there were 422 million of diabetic patients worldwide in 2014 in comparison to the 108 million cases in 1980. Thus the prevalence of diabetes has risen to 8.5% from 4.7% during 1980-2014. International Diabetes Federation (2015) estimates, there will be 642 million diabetes patients by the year 2040^{3,4}

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According to International Diabetes Federation South-East Asia (IDF SEA) there were 1.16 million patients with diabetic Mellitus in Sri Lanka.⁵

Anaemia is defined by the World Health Organization (WHO) as hemoglobin values <13 g/dL in men and <12 g/dL in women. ⁶

Anaemia of chronic disorder is a common cause of anaemia. The pathophysiology is multifactorial and involves an inability to use the available iron for red cell production.

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Diseases that can lead to Anaemia chronic disorder include, Autoimmune disorders such as systemic lupus erythematosus, Crohn disease and rheumatoid arthritis, malignancies, long-term infections, such as HIV/AIDS, hepatitis B or hepatitis C, bacterial endocarditis and osteomyelitis. Chronic diseases such as kidney failure and diabetes mellitus. ⁷

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Treatment for anaemia of chronic disorder involves proper management of the underlying disease. This type of anaemia is generally mild. So usually transfusions are not required.

Anaemia is a frequent condition in patients with T2DM and almost a quarter of diabetic patients are reported as anaemic. ⁸

Anaemia in diabetes has complex and multifactorial aetiology including reduced erythrocyte half-life, impaired production of erythropoietin, renal denervation, certain drugs and nutritional deficiencies. ^{9,10}

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Also anaemia can contribute to development and progression of diabetes-related micro and macro vascular complication in diabetes patients. ⁸

Serum ferritin level can be used to identify iron deficiency anemia from other types of anemia. Normally ferritin in plasma is present in small quantities, but it is directly proportional to the stored iron concentration in the body. Low concentration of ferritin is specific for iron deficiency anemia and also normal or high values may present in Anemia chronic disorder. ¹¹

Comment [VP17]: Need language correction

There are no studies indicating the prevalence of anaemia in T2DM patients in Sri Lanka. Hence we are not aware of the magnitude of the problem. Our study is designed to achieve an insight into the current situation in Sri Lanka.

The causes for anemia in Diabetes include Anemia of chronic disorder , anemia of renal origin, nutritional anemias including iron deficiency and Vit B12/Folate deficiency and haemoglobinopathy.No studies are available in Sri Lanka describing the causes of anemia in diabetes.

Data from studies around the world show varied prevalence of Anaemia in Patients with T2DM.

Anaemia was present in varying prevalence in studies in India from 12.3%¹², 18%¹³, 18.09%¹⁴ 37%¹⁵. Although one study showed similar occurrence between women (18.60%) and men (17.54%)¹³ most showed a female preponderance 11% of males and 16% of females^{14,16}.

Other prevalence studies showed 22% in China with a female preponderance (male 19.1% , female 25.8%)⁸, 63% (females-36%, males-27%) in Pakistan¹⁷, 22.8% in Hong Kong¹⁸, 39.4% in Malaysia¹⁹, 23% in Australia²⁰, 34.4% in Tehran²¹, 55.5% in Saudi Arabia²², 19.6% in Iran with higher female prevalence²³ and 59% in the United Kingdom.²⁴

Most had normocytic normochromic anaemia^{21,19}. Duration of diabetes and older age had significant correlation with anaemia.²⁴ and there was a significant association among micro vascular complications and prevalence of anaemia.²¹

Methodology

Descriptive cross sectional study carried out at the Diabetic clinic in Family Medicine Center, University of Sri Jayewardenepura.

All Patients with T2DM who attended the Diabetic clinic at the Family Medicine Center, University of Sri Jayewardenepura were included in the study.

Sample size was calculated by using equation given below.

$$n = z^2 p(1-p)/d^2$$

n = sample size

z = standard normal deviate for a chosen confidence level is 95% (1.96)

p = expected proportion of the anemia in patients with type 2 Diabetes Mellitus for Sri Lanka there is no published data for this category, so we have taken data from a research which conducted in India $p=0.123^{24}$ [12]

d = the precision to which the estimate is needed and it taken as 5% (0.05)

n = 166

However the sample size was limited to 102 as it was restricted to the T2DM patients receiving care at the Family Practice Centre.

Sampling and data collection:

Patients with T2DM were identified from the medical records. Volunteers were consented and a K₃EDTA anticoagulated blood sample for Full Blood Count was collected from each participant.

An interviewer administered questionnaire was filled and medical records perused of each participant to gather demographic information ,data pertaining to the disease (duration, complications , treatment) ,laboratory results of tests used to monitor disease (FBS, S. creatinine, HbA1C)

Blood samples were analyzed by using an automated cell analyzer. The Full Blood Count reports were analyzed and hemoglobin values, MCV, MCH and MCHC values were

tabulated for each patient. Quality control samples for the analyzer were run with the samples ensuring reliable reproducible results.

Patients with low hemoglobin value were selected and a non anticoagulated blood sample was collected for serum Ferritin.

Patients with red cell indices suggestive of haemoglobinopathy were reviewed by Blood picture and HPLC was done for confirmation.

Data analysis:

Socio demographic data and laboratory results were recorded and data analysis using SPSS (Statistical Package for Social Science) to detect the proportion and percentages.

Ethical consideration

Ethical clearance was obtained from the Ethical Review Committee of Faculty of Medical Sciences, University of Sri Jayewardenepura. Voluntary informed written consent was obtained from all participants. De identified data was used for study analysis

Results and analysis

A total of 102, T2DM patients were analyzed. 30 (29.4%) were males and 72 (70.6%) were females. (Figure 1) The mean age was 62.68 ± 12.26 years. The majority of the population was Sinhalese (99.0 %) and living in urban areas.

Comment [VP18]: After . better to use word rather number

Comment [VP19]: Reason for female preponderance, why urban

The recent mean fasting glucose level of the study population was 151.89 ± 71.29 mg/dL. The percentage of patients who had diabetes < 5 years was 43.1% and > 5 years was 56.9% and mean duration of diabetes was 9.57 ± 7.49 years.

90.2% of patients were on oral hypoglycemic agents, 1% was on insulin and 8.8% were on combined insulin and oral agent treatment.

7 patients (6.9%) had chronic kidney diseases 2(2%) had retinopathy and 2(2%) had diabetes related foot ulcers. The clinical characteristics of the total study population were analyzed and are presented in Table 1.

Comment [VP20]: Which oral hypoglycemic drug the study cases were on needs a mention

Comment [VP21]: Was erythropoietin given to these patients/ or estimation of erythropoietin done

Variable	Frequency (n=102)	Percentage (n=102)
Duration of DM		
1-5 years	44	43.1%
>5 years	58	56.9%
Type of medication		
Oral hypoglycemic agents	91	89.21%
Insulin	02	1.96%
Combined insulin and Hypoglycemic agents	09	8.82%
Presence of Chronic kidney disease	07	6.86%
Presence of diabetes retinopathy	02	1.96%
Presence of diabetes related foot ulcers	02	1.96%

Table 1: Summary of clinical characteristics

Mean Hb of the study population was 11.98 ± 1.79 g/dl (12.92 ± 2.49 g/dl in males and 11.60 ± 1.24 g/dl in females). The minimum Hb value was 6.3 g/dl and maximum Hb value was 17.5 g/dl in the study population. The patients were divided into non-anemic and anemic groups using normal ranges for males (12.5g/l) and females (11.5g/l).

Comment [VP22]: Was RBC count done In high Hb study subjects

The overall prevalence of anemia was 35.3% (36/102). This included 5 males (16.67% of male patients) and 31 females (43.05% of the female patients).

Serum ferritin level was assayed for all anemic patients and 04 anemic patients had low serum ferritin level. (Normal serum ferritin level was taken as 18-270 ng/ml for male and 18-160 ng/ml for female)

Comment [VP23]: Any comorbid conditions ruled out

Among anemic patients, normocytic anemia was present in 77.88% (28/36) of anemia; 07 of them had evidence of CKD and majority (21) was anemia of chronic disorder. Microcytic anemia was found in 22.22% (08/36); 04 of them had iron deficiency and 04 had thalassemia minor. There was no Macrocytic anemia found.

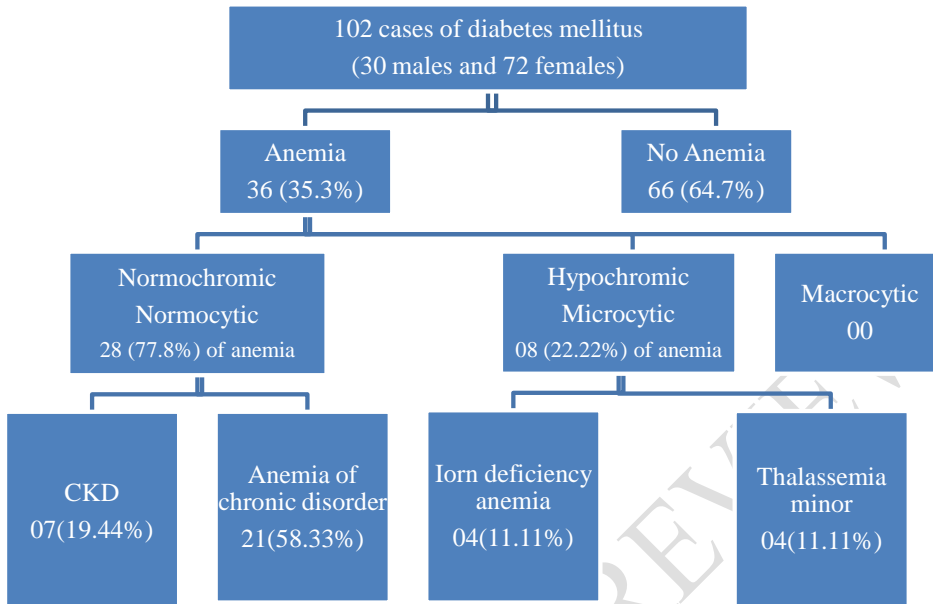


Figure 1: The etiological subtypes of anemia seen among T2DM in this study

Presence of anemia was significantly related to Age, Gender, Duration of DM and presence of CKD.

Among the male patients of study population, 16.67% (5/30) were anemic, and 43.06% (31/72) of the female patients were anemic. Significant association was found between gender and anemia in diabetics ($p=0.01$).

Comment [VP24]: Was peripheral smear done and estimation of Vitamin B12, folic acid done

Prevalence of anemia was 19.35% among adults who aged 50 -59 years, 41.6% for those aged 60-69 years, and 55.55% for those aged 70 years and older.

The presence of anemia was significantly related to increasing age ($p=0.036$)

There was a significant relationship between duration of DM and presence of anemia. Out of the 36 patients of anemia with DM, 28(77.8%) patients had DM for more than 5 years duration and 08 (22.2%) patients had DM for less than 5 years duration (p=0.002).

Comment [VP25]: What about HbA1c levels, stool for cyst and Ova was it done

86.1% of anemic patients were used oral hypoglycemic agents while 13.9% anemic patients were used combined oral hypoglycemic agents with insulin therapy. There was no significant association of mode of treatment with anemia (p=0.322).

The correlation between the duration of oral metformin usage and the presence of anemia among diabetes was not statistically significant (p=0.092)

In this study 19.4% of the anemic patients had evidence of CKD. There was a significant association with anemia and CKD. (p =0.000). Retinopathy was found in 5.6% anemic patients. However ,retinopathy does not having a significant association with anemia (p=0.05).

Variables	Anemic n=36 (35.3%)	Non Anemic n=66 (64.7%)	P value
Gender			
Male	5 (16.67%)	25 (83.33%)	0.01
Female	31(43.06%)	41 (56.9%)	

Age			
30-39 years	0 (0%)	1(100%)	
40-49 years	0 (0%)	4(100%)	
50-59 years	6 (19.4%)	25 (69.4%)	0.036
60-69 years	20 (41.6%)	28(58.3%)	
>69 years	10 (55.6%)	8 (44.4%)	
Duration of DM			
1-5 years	8 (18.1%)	36(81.8%)	0.002
>5 years	28 (48.3%)	30(51.7%)	
Type of medication			
Oral hypoglycemic agents	31(33.7%)	61(66.3%)	
Insulin	0 (0%)	1(100%)	0.322
Combined insulin and Hypoglycemic agents	5 (55.6%)	4(44.4%)	
Presence of diabetes retinopathy	2 (100%)	0(0%)	0.05
Absence of diabetes retinopathy	34(34%)	66(66%)	
Presence of Chronic kidney disease	7 (100%)	0(0%)	0.000
Absence of Chronic kidney disease	29(30.52%)	66(69.47%)	

Table 2: Frequency of various variables and their association with anemia

Comment [VP26]: Laboratory parameters needs to be presented as table

Discussion

Anaemia frequently complicates T2DM and contributes to progression of micro and macrovascular complications.²⁵ Although many studies have been done worldwide to ascertain the prevalence of anaemia in T2DM there are no published data available in Sri Lanka. In this study, we aimed to detect prevalence of anaemia, types of anaemia among patients with DM and describe any association to factors such as age, gender, duration of DM, medications and complications.

102 patients confirmed as T2DM were enrolled and the prevalence of anaemia was 35.29% (36 out of 102). Our study results correlate with the findings of Makadiya R. et al found who reported that 37 of 100 patients (37%) with diabetes had anaemia in India.²⁶ However it was significantly higher than the prevalence reported in two other studies which reported prevalence of 18%²⁷ and 12.3%¹². This could be due to the vast differences in population demographics over India. Our percentages are matched to that of prevalence found in studies in other countries such as Bagdad 39%³⁵, Malaysia 39.4%¹⁹, Tehran 34.4%²¹ and Northern California 34.7%³⁶. But higher than Australia 23%²⁰, Iran 19.6%²³ China, 22%²⁴ and Hong Kong 22.8%¹⁸.

It was lower than that reported than 55.5% in Saudi Arabia²² 59% in the United Kingdom, and 63% in Pakistan¹⁷

On classification according to MCV and MCH, Normochromic normocytic type is the most common type (77.78%) among anaemic patients while 22.22% were hypochromic microcytic. This corresponds to any studies where Normochromic normocytic anaemia was the most prevalent when classified morphologically.^{19, 21, 35}

Serum ferritin was done on all of the patients with anaemia and was normal in 32 patients. Thus a majority of patients have anaemia of chronic disorder, which is expected to be the most frequent cause for anaemia in T2DM. 04 patients had low Serum ferritin and hypochromic microcytic indices and were diagnosed as iron deficiency anaemia. Samples of blood of 04 (11.11%) with red cell indices suggestive of thalassemia trait were subjected to HPLC and a diagnosis of Beta Thalassemia Trait was made.

Our results indicate, that the presence of anaemia was significantly related to age, gender and duration of DM and presence of CKD. But the correlation between anaemia and the duration of oral metformin usage is not statistically significant.

In the present study anaemia was observed in 05 male and 31 female patients suggesting that risk the of anaemia in patients with T2DM is significantly affected by gender ($p < 0.05$). This correlates well with findings of Makadiya R. et al who showed that 26 % of male diabetic patients and 62% of females were classified as anaemic and the difference was significant.²⁶ Shams N. et al also found that Females were more prone to be anaemic than male patients, but the difference was not significant ($P = 0.154$).²⁵

ArtzA. S. has stated that Hb drops slightly and anaemia prevalence increases in males and females with advancing age.²⁸ The present study also proves the above finding.

($p = 0.036$). The prevalence of anaemia was 19.35% among adults aged 50 -59 years, 41.6% for those aged 60-69 years, and 55.55% for those aged 70 years and older. This correlates with other studies done to establish the presence of anaemia with age in DM patients. Abate A. et al have showed that there is a significant correlation with increased age and association of anaemia among T2DM patients.²⁹ Fayed H. M. et al found the prevalence of anaemia was

87.3% among T2DM patients with >45 years age and 12.7% among T2DM patients with <45 years, while 94.6 % T2DM patients were non-anaemic with age >45 years and 5.4% with age <45 years.³⁰

As expected, there was a significant correlation between anaemia and the duration of DM. 44 patients in this study had DM for less than 5 years (48.3%). Among those, 8 patients had anaemia (18.2%). Out of the patients who had DM for more than 5 years, 28 were anaemic (48.3%). Based on data in the current study, there is a 2.65 times higher risk of getting anaemia after 5 years of onset of diabetes. According to the study by RathodG. et al, a 1.56 times higher risk of anemia in diabetes after 5 years is reported. .²⁷

In the current study,86.1% of anemic patients used oral hypoglycemic agents while 13.9% anemic patients were treated with combined oral hypoglycemic agents and insulin therapy. However there was no significant correlation between mode of treatment and prevalence of anemia among patients with DM ($p=0.322$). This correlates with the finding of Shams N. et al who also has stated that there was no significant correlation between mode of treatment and anemia ($p=0.382$).³¹

Metformin is the most widely used treatment for people with T2DM. In this population it was 94.12%. This medication is known to cause malabsorption of vitamin B₁₂, which causes vitamin B₁₂ deficiency and it can be lead to macrocytic anemia.³² ThambiahS.C. et al found 3.1% of patients who using metformin had macrocytic anemia.¹⁹ But in the current study, there were no patients with macrocytic anemia. This result may be due to the fact that most diabetics are supplemented with vitamin B₁₂.

Reduced Hb values may be caused by the presence of CKD due to diminution of erythropoietin. Thomas M. et al said that anaemia could be used as an early predictor for reduction of renal function in diabetes.³³ According to shams N. et al, prevalence of anaemia

in diabetic patients with CKD was 50%.³¹ In the present study, 7 patients had diabetes related kidney disease and all of them were diagnosed as anaemic. Al salmon said that, 64.7% with impaired renal function had anaemia among DM patients in their study.³⁴ In this study, we used only available clinical data to identify CKD but most patients were not screened for CKD previously. Our results might be changed if GFR, Serum Creatinine, Albumin urea, EPO level & other related tests were performed.

Comment [VP27]: To be shown as graphs or tables

According to Shams N. et al there was a significant correlation between anaemia and diabetic retinopathy.³¹ In present study, 5.5% of anaemic patients had diabetes related retinopathy. However the association between anaemia and diabetic retinopathy was not significant. This may be due to the small number of subjects analyzed.

Limitations

The sample size was limited as the study was restricted to the Diabetic clinic of Family Medicine Center, Faculty of Medical Sciences, University of Sri Jayewardenepura and therefore we could not collect the expected. The study population only represented the suburbs of the University of Sri Jayewardenepura. If more patients from other diabetic clinics were enrolled in the study the sample size could have been increased.

Conclusion

Findings from current the study suggest that anemia is present in a significant proportion of T2DM (35.29%) . Anemia of chronic disorder(inclusive of anaemia of renal disease) is the most frequent type of anemia (77.78%) with a smaller percentage diagnosed as iron deficiency(11.11%) and haemoglobinopathy (11.11%).The presence of anemia is significantly associated with increasing age, female gender, duration of diabetes mellitus and

presence of CKD. Therefore anemia detection should be included in to tests done for routine management of T2DM. As the treatment of anemia of chronic disorder is treatment for the underlying disease proper management of diabetes will reduce the prevalence of anemia in this group. It will also help to minimize the risk of microvascular and macrovascular complications and enhance the life quality of T2DM patients.

Declarations

- **Availability of data and materials** patient de identified raw data are with the researchers can be made available.
- **Competing interests** No competing interest
- **Funding** Not applicable
- **Authors' Contribution**

BF: conceptualization of the research, editing of the research proposal through all stages, writing up the manuscript, editing and formatting manuscript to journal specifications. **SS:** Supervising data collection, editing final version of manuscript **MWND, HTNB:** Writing the project proposal, data collection and analysis, writing the project report. All authors have read and approved the final manuscript.

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Comment [VP28]: For all reference uniformity needs to be maintained, DoI, Vancouver style to be followed or as per the journal specifications

UNDER PEER