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# The degree to which anemia and micro or macrovascular problems are correlated Problems with Patients with Type 2 Diabetes Mellitus in India

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**ABSTRACT:**

**Objective and AIM:** The majority of diabetes patients in India are not assessed for anemia until clinical signs of renal impairment manifest. It has recently been shown that anemia may have a role in the development of microvascular complications in patients with type 2 diabetes. The main aim of the study was to assess whether anemia in Chinese patients with type 2 diabetes mellitus (T2DM) is associated with micro- and macrovascular problems.

**Material and Methods**: 150 patients with Type 2 Diabetes who were attending Medical OPD in Kolkata and the surrounding areas were included in this cross-sectional study. Every patient had a thorough evaluation of their risk factors and problems connected to diabetes at the time of admission. Patients with a diagnosis of type 2 diabetes and anemia (Hb level >10 gm/dl) are eligible to apply. Patients with hemolytic anemia, aplastic anemia, acute blood loss, severe infection, collagen disease, and type 1 diabetes or other forms of diabetes are excluded. To determine whether anemia and diabetes and its consequences are related, appropriate statistical analysis was conducted.

**Results**: Ninety-nine (72 males and 27 females) of the 150 diabetes participants in the study were anemic and fifty-one (34 males and 17 females) were non-anemic. Haemoglobin levels significantly decreased after three years of diabetes, according to the results. The anemic group had higher rates of neuropathy (77%), retinopathy (38%), CVA (12%), and CAD (21%), compared to the non-anemic group. While microalbuminuria exhibited the opposite pattern, the incidence of neuropathy and retinal disease rose as anemia severity increased. The group with mild anemia had the highest incidence of CAD, PVD, and CVA. According to the TIMI score, anemia severity raises the mortality risk in coronary artery disease (ischemia).

**Conclusion**: According to our findings, anemic patients were more likely than non-anemic patients to have microvascular sequelae, such as diabetic neuropathy, diabetic nephropathy, and diabetic retinopathy. We can therefore draw the conclusion that anemia may have a role in the development of microvascular complications in people with type 2 diabetes.

## Introduction:

Because life expectancy has increased, diabetes is becoming more and more common [1]. As a collection of metabolic illnesses, diabetes mellitus has serious microvascular consequences that cause morbidities prior to diagnosis. According to a number of studies, between 5% and 35% of people with diabetes are thought to have microvascular problems [2–5].

Anaemia, serum albumin, albuminuria, and serum creatinine are the main risk factors for microvascular problems [6]. People with diabetes are more likely than people without diabetes to experience anemia, a common consequence [7]. Compared to the general population, DM patients typically experience anemia at younger ages and with more severe symptoms [8]. Tissue hypoxia brought on by chronic anemia is known to be a major factor in the organ damage linked to diabetes. However, these people have anemia as a result of chronic kidney disease. Even before chronic renal disease develops, anemia exists [9,10]. According to a study conducted in Iran, 10% of patients with type 2 diabetes were predicted to have anemia [11]. Anaemia before renal failure should lead to a more thorough evaluation and treatment in order to lower morbidity and mortality from the microvascular consequences, even if it is a sign of diabetic nephropathy.

Severe anemia can also impact the outcome of heart failure and hypoxia-induced organ damage in diabetic individuals [12]. Presence of anemia itself has its own consequences such exercise intolerance, poor growth, low cognition and poor appetite. Anaemia can result in an artificially low level of

glycosylated haemoglobin (HbA1c), which can cause hyperglycemia to go undiagnosed and diabetes-related micro- and macrovascular problems to continue to worsen. Therefore, more clinical trials investigating the management of anemia in diabetes patients are essential [13].

Despite the prevalence of diabetes-related anemia and its known implications, there are very few publications on the association between the length of diabetes and anemia. Therefore, it is unknown how anemia and vascular problems relate to each other in patients with type 2 diabetic mellitus (T2DM). In order to determine the prevalence and severity of anemia with micro- and macrovascular consequences in T2DM patients who routinely visit the hospital for blood glucose testing but do not exhibit obvious signs of renal disease, we undertook a cross-sectional study.

## Material and Methods:

**Study type:** This was can observational real world cross sectional study. Patients who were OPDs at our diabetic clinic participated in this study. Each patient's information was gathered using a pre-made and pre-tested proforma. A thorough history, clinical examination, biochemical analysis, and ocular evaluation were performed on qualified individuals.

**Inclusion & Exclusion criteria:** Patients with type 2 diabetes who attended the diabetic outpatient department and were between the ages of 20 and 70 were included in this study. This study also included patients with a recent diagnosis of type 2 diabetes. The trial excluded subjects with severe infections, acute cerebrovascular disease, severe impaired hepatic function (AST or ALT>2×upper limit of normal), recent surgery, patients with any malignancy, patients with HIV-AIDS, and those with type 1 diabetes mellitus, gestational diabetes, CKD stage 3-5, CCF, and causes of anemia such as aplastic anemia, hemolytic anemia, or thalassaemia.

**Methods:** In 2015, the National Kidney Foundation established criteria for the presence of chronic kidney disease, while the American Diabetes Association established criteria for the presence of diabetes mellitus. BMI is determined using the most recent WHO recommendations. According to WHO guidelines, anemia was defined as Hb < 13 g/dL in men and < 12 g/dL in women. Every patient had a thorough evaluation of their risk factors and problems connected to diabetes at the time of admission. The MDRD Formula's GFR estimation and the albuminuria urine test were used to classify diabetic neuropathy (DN). If the patient's 24-hour albumin excretion was less than 30 mg/g, micro-albuminuria if it was between 30 and 300 mg/g, or macro-albuminuria if it was greater than 300 mg/g, they were classified as normo albuminuric. Participants with macroalbuminuria were not included in the study. The Michigan Neuropathy Screening Instrument was used to assess diabetic neuropathy (DPN). A score greater than two indicated the presence of neuropathy. All patients with diabetic retinopathy (DR) were referred to an ophthalmologist, who assessed the extent of eye involvement, taking into account both proliferative and non-proliferative diabetic retinopathies. Fundoscopy was used to do an ophthalmologic examination with dilated pupils. If the patient presented a typical ischemic history or ECG abnormalities that suggested ischemia, coronary artery disease (CAD) was assumed to be present. Transient ischemic attacks or strokes were used to diagnose cerebrovascular disease (CVD). Ankle-Brachial Index evaluation and a history of claudication pain were used to diagnose peripheral artery disease. Diabetic macrovascular problems included CAD, CVD, and PVD, while diabetic microvascular complications included DR, DN, and DPN.

**Statistical analysis:** SSPS statistical software (SSPS version 21. Inc., Chicago, IL, USA) was used to conduct the statistical study. The mean and standard deviation for continuous data and percentages for categorical variables were used to report patient demographics. Continuous variables between the two groups were compared using the independent sample t-test, while categorical variables were compared using chi-square. The threshold for statistical significance was set at 5% ($p < 0.05$). Microsoft Word and Excel were used to create the graphs, tables, and other graphics.

## Results:

99 anemic (72 males and 34 females) and 51 non-anemic (27 males and 17 females) of the 150 diabetic participants in the study lived. The non-anemic group's mean age was 58.62 ± 14.69 years, while the anemic group's was 64.32 ± 14.32 years. 18 (35%) in the control group were between the ages of 51 and 60, whereas the largest number of patients (32%) in the anemia group, or 32 patients, were between the ages of 61 and 70. Table 1 describes the overall characteristics of the study population. In comparison to the control group, the case group's mean BMI was higher, and the difference was statistically significant ($p = 0.032$). Additionally, the anemic group had a higher mean systolic blood pressure.

The haematological parameters of the blood samples we examined that were taken from the research participants are displayed in Table 2. It was found that the cases' Hb concentration was considerably lower than the controls'. 9.02 ±1.67 g/dl was the mean Hb concentration (8.23 g/dl in males and 7.84 g/dl in females). Compared to the controls, the cases' serum iron levels were noticeably lower. Compared to the control group, ferritin and total iron-binding capacity (TIBC) levels were shown to be in the lower range.

**Table 1: The research groups' general attributes and biochemical profiles**

| Variables | Group A (Anemia) (N=99) | Group B (non-anemia) (N=51) | P Value |
|---|---|---|---|
| Gender | | | |
| Male | 72 (72.7%) | 34 (66.6%) | NA |

| | | | |
|---|---|---|---|
| Female | 27 (27.3%) | 17 (33.3%) | |
| Age (in yrs.) | 64.32 ± 14.32 | 58.62 ± 14.69 | 0.031* |
| Duration of Diabetes | 14.12 ± 11.16 | 7.28 ± 5.48 | 0.001*** |
| BMI ($kg/m^2$) | 28.23 ± 5.11 | 24.73 ± 4.14 | 0.032* |
| SBP (in mmHg) | 141.17 ± 15.41 | 130.83 ± 11.52 | 0.008** |
| DBP (in mmHg) | 87.41 ± 7.21 | 83.74 ± 11.29 | |
| Haemoglobin (g/dl) | 8.78 ± 0.94 | 14.01 ± 1.14 | 0.000 |
| HbA1c (%) | 8.12 ±1.34 | 7.49 ± 1.26 | 0.372 |
| S. Iron | 42.39 ±24.18 | 62.67 ± 30.12 | 0.002 |
| TIBC | 279.32 ± 65.22 | 321.42 ± 81.42 | 0.294 |
| S. Ferritin | 178.51 ± 121.73 | 231.62 ± 131.32 | 0.392 |
| S. Vitamin $B_{12}$ | 322.46 ± 178.13 | 342.57 ± 171.81 | 0.731 |

**Values presented as Mean± SD or No. (%). Test applied chi-square; student t test *Significance* p<0.05;**p<0.01;***P<0.001**

Table 2 displays the trend of haematological parameter changes over the course of diabetes. Several combinations of diabetes duration were created as subgroups, and numerous comparisons were performed for each combination in order to determine the earliest duration of diabetes that may result in statistically significant low mean haemoglobin levels. The subgroup combinations of up to three years, three to ten years, and more than ten years produced statistically significant findings.

**Table 2: Comparison of the case group's several anemia metrics with the length of their diabetes**

| **Characteristics** | **Anemia (N=99)** | | | **P Value** |
|---|---|---|---|---|
| | **< 3 Years (N=22)** | **3-10 Years (N=25)** | **>10 Years (N=52)** | |
| Hb | 9.21 ±1.93 | 9.08±1.23 | 8.61 ±1.42 | 0.038* |
| HbA1c | 9.02 ±1.67 | 7.92± 1.51 | 8.14±1.39 | 0.271 |
| Serum Iron | 54.42 ±29.83 | 51.21 ±25.48 | 41.23 ±14.73 | 0.0648 |
| TIBC | 372.92 ±69.68 | 362.32 ±59.21 | 229.62 ±49.93 | 0.000*** |
| Serum Ferritin | 221.32 ±142.31 | 159.74 ±139.84 | 179.81 ±119.26 | 0.672 |
| Serum Vitamin $B_{12}$ | 319.42 ±189.41 | 311.6 ±191.12 | 309.98±181.123 | 0.873 |

**Test applied-ANOVA**
**Significance* p<0.05;**p<0.01;***P<0.001**

Haemoglobin levels significantly decreased after three years of diabetes, according to the results. The change was statistically significant, and the mean iron levels likewise gradually decreased. Additionally, as the length of diabetes grew, the mean TIBC levels decreased. Males and females had varied outcomes (Table 4).

**Table 3: Comparison of various anemia metrics between male and female participants with diabetes duration**

| **Variables** | **Gender** | **Duration of Diabetes (in years)** | | |
|---|---|---|---|---|
| | | **< 3 years** | **3- 10 years** | **>10 years** |
| Hb | Male | 11.21±1.73 | 9.39±1.23 | 9.71±1.63 |
| | Female | 10.12±1.84 | 8.52±1.36 | 8.02±1.04 |
| S. Iron | Male | 58.64±18.53 | 53.34±20.78 | 41.48±11.82 |
| | Female | 48.54±32.73 | 37.26±32.62 | 27.6±18.31 |
| TIBC | Male | 318.64±39.25 | 351.21±53.84 | 229.42±57.51 |
| | Female | 391.25±82.47 | 379.63±72.23 | 229.61±60.42 |

The study group's micro and macrovascular problems are displayed in Table 4 accordingly. Of the 99 patients in group A, 66.67% had microalbuminuria, 40% had retinopathy, and 75.76% had neuropathy. The anemic group had a higher prevalence of neuropathy (75 instances, or 75.76%) than the control group (21 patients, or 41.1%), followed by retinopathy, which also showed a statistically significant difference. There was a notable difference in the incidence of CVA between the control and case groups. Compared to patients without anemia (13.73%), diabetic patients with anemia had a higher prevalence of myocardial ischemia (20.20%). Compared to 3 (4%) patients without anemia, 12 diabetic patients with anemia (12.12%) experienced a stroke. (Table 4).

**Table 4: Comparison of the research groups' microvascular complications**

| **Types of Complication** | | **Group A (Anemia) (N=99)** | **Group B (non-anemia) (N=51)** | **P Value** |
|---|---|---|---|---|
| Microvascular complication | Retinopathy | 40 (40.44%) | 8 (15.68%) | 0.005** |
| | Neuropathy | 75 (75.76%) | 21 (41.17%) | 0.000*** |
| | Micro albuminuria | 66 (66.67%) | 29 (56.86%) | 0.983 |
| Macrovascular Complications | Myocardial Ischaemia | 20 (20.20%) | 7 (13.73%) | 0.572 |
| | PVD | 4 (4.04%) | 2 (3.92%) | 0.947 |
| | CVA | 12 (12.12%) | 3 (4.09%) | 0.863 |

**Test applies-Chi-square test. Significance* p<0.05;**p<0.01;***P<0.001**

The frequency of micro and macrovascular problems with the length of diabetes is shown in Table 5. The group with a duration of more than ten years experienced the greatest number of problems.

**Table 5: Diabetes complications over time**

| **Complications** | **Duration of Diabetes (in years)** | | | **Total** |
|---|---|---|---|---|
| | **< 3 years** | **3- 10 years** | **>10 years** | |
| Retinopathy | 0 | 0 | 48 | 48 |
| Neuropathy | 19 | 29 | 48 | 96 |
| Microalbuminuria | 16 | 28 | 51 | 95 |
| CVA | 2 | 4 | 9 | 15 |
| MI | 5 | 4 | 18 | 27 |
| PVD | 1 | 2 | 3 | 6 |

Both microvascular and macrovascular complications were associated with the severity of anemia (Table 6). While microalbuminuria exhibited the opposite pattern, the incidence of neuropathy and retinopathy rose as the degree of anemia increased. The group with mild anemia had the highest incidence of CAD, PVD, and CVA.

**Table 6: Anemia severity combined with diabetes complications**

| **Haemoglobin** | **Neuropathy** | **Retinopathy** | **Micro albuminuria** | **CAD** | **CVA** | **PVD** |
|---|---|---|---|---|---|---|
| Non Anemic | 18 | 5 | 26 | 3 | 3 | 0 |
| Mild Anemia | 24 | 8 | 21 | 5 | 2 | 1 |
| Moderate Anemia | 46 | 21 | 40 | 17 | 10 | 4 |
| Severe Anemia | 8 | 14 | 8 | 2 | 0 | 1 |

Table 7 demonstrate assessment of anemia severity using the TIMI score for cardiovascular mortality. TIMI (AVG) was highest in severe anemia group while it was minimum in non anemic group.

**Table 7: Assessment of anemia severity using the TIMI score for cardiovascular mortality**

| **Haemoglobin** | **STEMI** | **NSTEMI** | **TIMI (AVG)** |
|---|---|---|---|
| Mild Anemia (5) | 4 | 1 | 4.5 |
| Moderate Anemia (12) | 9 | 3 | 6 |
| Severe Anemia (2) | 1 | 1 | 9 |
| Non Anemic (7) | 5 | 2 | 4.4 |

## Discussion:

By eliminating patients with overt nephropathy (CKD grade IV, V, or mega albuminuria), we have attempted to compare the severity of anemia with the sequelae of diabetes in this study. We have also attempted to link the length of diabetes with the occurrence of anemia and its complications.

Globally, and especially in India, the prevalence of diabetes mellitus is sharply increasing. According to the International Diabetes Federation (IDF), there were approximately 40.9 million diabetic persons in India in 2006; by 2025, that number is expected to increase to 69.9 million [14]. Anemia is frequently linked to diabetes and may have a role in the development of complications from the disease [15].

Of the 150 diabetic participants in our study, 99 case subjects (72.7% males and 27.3% females) were anemic, while 51 controls (66% males and 33% females) were not anemic. According to Trevest et al., anemia is common in older diabetics [16]. Anemia rates among individuals with diabetes who did not have renal insufficiency were 15.3%, according to a prior study [17]. According to the study, people with poorly managed diabetes had a higher risk of anemia than those with well-controlled diabetes. Anemia was found in 7.2% of diabetics with normal renal function, according to another study [18]. Overweight was highly prevalent in this study, and anemic patients' mean BMI was considerably greater than that of the non-anemic group (p=0.032). Particularly in adipocytes and muscle cells, obesity is linked to the development of an inflammatory state, which raises blood glucose circulation and causes a hyperglycaemic state [19]. More recently, adipose tissue has been identified as an organ system that links the immune and endocrine systems and is metabolically active. It also produces a range of cytokines [20].

Our study also revealed that diabetes individuals who were anemic had considerably higher systolic blood pressure and diabetic blood pressure than those who were not anemic. Given that hypertension in diabetes mellitus raises the risk of cardiovascular problems like heart failure, stroke, atherosclerosis, and tissue inflammation, this relationship is concerning [21].
Anemia is a common co-morbidity in patients with hypertension, and when it occurs, patients have worse functional ability, more severe symptoms, and a higher mortality rate [22]. Although it has long been known that anemia exacerbates the symptoms of hypertension, the extent of the link between anemia and this condition has lately come to light.

Chronic inflammation and dietary deficits, particularly those involving iron, are the primary causes of anemia in people with hypertension. According to the current study, lower serum iron levels were linked to the anemic group's low haemoglobin levels. Additionally, it was discovered that the anemic group's total iron binding capacity was below the normal range, which is indicative of anemia of chronic disease (ACD). ACD is immune-driven; reticuloendothelial system cells and cytokines alter iron homeostasis, erythroid proginator cell proliferation, erythropoietin synthesis, and red blood cell life span, all of which contribute to the pathophysiology of anemia. Through tumour cell infiltration into bone marrow or microorganisms, diseases that underlie anemia in chronic conditions can impact erythropoiesis [23].

Even before renal impairment develops, diabetes mellitus, a chronic inflammatory disease, has elevated levels of pro-inflammatory cytokines. Diabetes-related anemia has a complex etiopathogenesis. The most common cause of anemia in diabetic patients is erythropoietin (EPO) insufficiency brought on by diabetic neuropathy [24,25]. However, a number of additional factors may contribute to the creation of a chronic hypoxic milieu, which may promote erythropoietic stress and intensify the genesis of early anemia in diabetes, even before any functional or organic deficit of EPO is apparent. Furthermore, renal denervation caused by autonomic neuropathy can reduce sympathetic activation of erythropoietin synthesis [26].

Our research indicates that in the diabetic population, the incidence of retinopathy and neuropathy rises as anemia severity increases. In contrast, the incidence of microalbuminuria falls as anemia severity increases, potentially as a result of an increase in overt nephropathy progression as anemia worsens, which was not included in the study.

Although the prevalence of macrovascular disease was higher in the anemic group than in the non-anemic group in our Type 2 diabetes cohort, the differences were not statistically significant. Additionally, these results did not align with previous research findings [27-30], and that indicated anemia as a separate risk factor for macrovascular disease. In one study [32], demonstrated that anemia was a strong risk factor for developing heart failure for the first time, while other studies demonstrated that anemia was a prognostic indicator for poor outcomes in patients with pre-existing heart failure [33]. According to Dries DL et al.[32], the higher prevalence of anemia in diabetic patients may be a factor in their poorer heart failure prognosis when compared to both non-anemic and non-diabetic individuals with anemia.

We used the TIMI score to evaluate the mortality of CAD patients in our study. We came to the conclusion that the TIMI score, or risk of death, rises with the degree of anemia. Anemia and diabetes together were linked to a considerable risk of death during a 36-month period, with over 65% of patients dying by that time, according to a study by David H. Shu et al.[32]. It has been demonstrated that anemia is well tolerated in hearts that are operating correctly. The reduced ability of blood to carry oxygen is compensated for by an increase in cardiac output, which is achieved through a higher heart rate, a bigger stroke volume, and a decrease in blood viscosity [34,35] Anemia may contribute to the increased long-term mortality in post-MI patients by exacerbating left ventricular dysfunction or ischemia.

There were few limitation in our study. First of all, it is still unclear how long diabetes lasts after anemia has started, so it is also unclear when to check for anemia. Second, the study's small sample size—particularly for macrovascular disease—led to equivocal findings. Better findings might have been obtained with a larger sample size. Erythropoietin (EPO) levels in people with diabetes and anemia may be abnormally low in comparison to those with iron deficiency anemia, according to some research [36].

## Conclusion:

Anemia is present in adults with normal renal function and is frequently linked to diabetic patients. Thus, they play a part in the development of vascular problems, both little and large. Additionally, anemia results in an erroneously low HbA1c estimate, which impairs diabetes management. Additionally,

as indicated by TIMI score, the severity of anemia raises the mortality risk in coronary artery disease (ischemia). In order to improve quality of life, anemia should be treated to reduce and postpone consequences, and it should be taken into consideration for regular management of patients with Type 2 diabetes.

**Availability of data and materials**

Datasets analysed during the current study available from the corresponding author on reasonable request.

**Authors contributions**

**Anwar Jamal**: Study concept and design, participated in literature bibliography, Acquisition of data, Analysis and interpretation of data, Drafting of the manuscript, Critical revision of the manuscript for important intellectual content. **Kausik Datta**: Drafting of the manuscript, Acquisition of data. MS: Drafting of the manuscript and Statistical analysis. **Aditya Mandal:** Drafting of the manuscript, Acquisition of data. MS: Drafting of the manuscript and Statistical analysis. **MG Alam**: participate in design of study and final revision of the manuscript.

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**Competing interests**

The authors declare that they have no competing interests.

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